



Coronavirus Disease 2019 (COVID-19) Treatment Guidelines

Credit NIAID-RML

How to Cite the COVID-19 Treatment Guidelines:

COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at <https://www.covid19treatmentguidelines.nih.gov/>. Accessed [insert date].

The COVID-19 Treatment Guidelines Panel regularly updates the recommendations in these guidelines as new information on the management of COVID-19 becomes available. The most recent version of the guidelines can be found on the COVID-19 Treatment Guidelines website (<https://www.covid19treatmentguidelines.nih.gov/>).

Table of Contents

What's New in the Guidelines	4
The COVID-19 Treatment Guidelines Panel's Statement on the Emergency Use Authorization of Anti-SARS-CoV-2 Monoclonal Antibodies for the Treatment of COVID-19..	6
The COVID-19 Treatment Guidelines Panel's Statement on the Use of Tocilizumab for the Treatment of COVID-19	12
Introduction	17
Overview of COVID-19	20
Testing for SARS-CoV-2 Infection.....	24
Prevention and Prophylaxis of SARS-CoV-2 Infection	30
Clinical Spectrum of SARS-CoV-2 Infection.....	39
Care of Critically Ill Patients With COVID-19.....	45
General Considerations	47
Infection Control	54
Hemodynamics.....	57
Oxygenation and Ventilation	60
Acute Kidney Injury and Renal Replacement Therapy.....	57
Pharmacologic Interventions	68
Extracorporeal Membrane Oxygenation	69
Therapeutic Management of Patients With COVID-19.....	71
Antiviral Drugs That Are Approved or Under Evaluation for the Treatment of COVID-19...	82
Remdesivir	84
Table 2a. Remdesivir: Selected Clinical Data	86
Chloroquine or Hydroxychloroquine With or Without Azithromycin	92
Table 2b. Chloroquine or Hydroxychloroquine With or Without Azithromycin: Selected Clinical Data	97
Ivermectin	109
Table 2c. Ivermectin: Selected Clinical Data	114
Lopinavir/Ritonavir and Other HIV Protease Inhibitors	125
Table 2d. Characteristics of Antiviral Agents That Are Approved or Under Evaluation for the Treatment of COVID-19.....	130
Anti-SARS-CoV-2 Antibody Products	135
Convalescent Plasma	136
Immunoglobulins: SARS-CoV-2-Specific	143
Anti-SARS-CoV-2 Monoclonal Antibodies.....	144
Table 3a. Anti-SARS-CoV-2 Monoclonal Antibodies: Selected Clinical Data.....	151
Table 3b. Characteristics of SARS-CoV-2 Antibody-Based Products Under Evaluation for the Treatment of COVID-19.....	158

Cell-Based Therapy Under Evaluation for the Treatment of COVID-19	161
Immunomodulators Under Evaluation for the Treatment of COVID-19	164
Corticosteroids.....	165
Table 4a. Corticosteroids Selected Clinical Data	170
Interferons (Alpha, Beta)	183
Interleukin-1 Inhibitors	185
Interleukin-6 Inhibitors	188
Kinase Inhibitors: Baricitinib and Other Janus Kinase Inhibitors, and Bruton’s Tyrosine Kinase Inhibitors	193
Immunoglobulins: Non-SARS-CoV-2-Specific	200
Table 4b. Characteristics of Immunomodulators Under Evaluation for the Treatment of COVID-19.....	202
Antithrombotic Therapy in Patients with COVID-19	215
Supplements	224
Vitamin C.....	225
Vitamin D.....	228
Zinc	230
Considerations for Certain Concomitant Medications in Patients with COVID-19	234
COVID-19 and Special Populations	238
Special Considerations in Pregnancy	239
Special Considerations in Children.....	243
Special Considerations in Adults and Children With Cancer.....	247
Special Considerations in Solid Organ Transplant, Hematopoietic Stem Cell Transplant, and Cellular Therapy Candidates, Donors, and Recipients	254
Table 5. Special Concerns for Drugs That Are Being Evaluated for COVID-19 Treatment in Transplant Patients	258
Special Considerations in People With Human Immunodeficiency Virus.....	260
Influenza and COVID-19	266
Appendix A, Table 1. COVID-19 Treatment Guidelines Panel Members	269
Appendix A, Table 2. Panel on COVID-19 Treatment Guidelines Financial Disclosure for Companies Related to COVID-19 Treatment or Diagnostics	271

What's New in the Guidelines

Last Updated: April 8, 2021

The *Coronavirus Disease 2019 (COVID-19) Treatment Guidelines* is published in an electronic format that can be updated in step with the rapid pace and growing volume of information regarding the treatment of COVID-19.

The COVID-19 Treatment Guidelines Panel (the Panel) is committed to updating this document to ensure that health care providers, patients, and policy experts have the most recent information regarding the optimal management of COVID-19 (see the [Panel Roster](#) for a list of Panel members).

New Guidelines sections and recommendations and updates to existing Guidelines sections are developed by working groups of Panel members. All recommendations included in the Guidelines are endorsed by a majority of Panel members (see the [Introduction](#) for additional details on the Guidelines development process).

Major revisions to the Guidelines within the last month are as follows:

April 8, 2021

[The COVID-19 Treatment Guidelines Panel's Statement on the Emergency Use Authorization of Anti-SARS-CoV-2 Monoclonal Antibodies for the Treatment of COVID-19](#)

Anti-SARS-CoV-2 monoclonal antibodies are available through Food and Drug Administration Emergency Use Authorizations (EUAs). Data are emerging on these monoclonal antibodies, including preliminary data from a Phase 3 trial of casirivimab plus imdevimab, and on the in vitro susceptibility of SARS-CoV-2 variants to anti-SARS-CoV-2 monoclonal antibodies. After reviewing the available data, the Panel has updated its recommendations on the use of anti-SARS-CoV-2 monoclonal antibodies in outpatients with mild to moderate COVID-19 who are at high risk of disease progression.

Based on the available evidence, the Panel has determined the following:

- The Panel recommends using one of the following combination anti-SARS-CoV-2 monoclonal antibodies to treat outpatients with mild to moderate COVID-19 who are at high risk of clinical progression, as defined by the EUA criteria (listed in alphabetical order):
 - **Bamlanivimab 700 mg plus etesevimab 1,400 mg (AIIa); or**
 - **Casirivimab 1,200 mg plus imdevimab 1,200 mg (AIIa).**
- Treatment should be started as soon as possible after the patient receives a positive result on a SARS-CoV-2 antigen or nucleic acid amplification test (NAAT) and within 10 days of symptom onset.
- There are no comparative data to determine whether there are differences in clinical efficacy or safety between bamlanivimab plus etesevimab and casirivimab plus imdevimab.
 - There are SARS-CoV-2 variants, particularly those that contain the mutation E484K, that reduce the virus' susceptibility to bamlanivimab and, to a lesser extent, casirivimab and etesevimab in vitro; however, the clinical impact of these mutations is not known.
 - In regions where SARS-CoV-2 variants with reduced in vitro susceptibility to bamlanivimab plus etesevimab are common, some Panel members would preferentially use casirivimab plus imdevimab while acknowledging that it is not known whether in vitro susceptibility data correlate with clinical outcomes.

- Because clinical outcome data are limited and there are concerns regarding decreased susceptibility of variants, the Panel **recommends against** the use of **bamlanivimab monotherapy (AIII)**.
 - If combination products are not available, the use of bamlanivimab monotherapy can be considered for people who meet the EUA criteria on a case-by-case basis.
- The Panel **recommends against** the use of **anti-SARS-CoV-2 monoclonal antibodies** for patients who are hospitalized because of COVID-19, except in a clinical trial (**AIIa**). However, their use should be considered for persons with mild to moderate COVID-19 who are hospitalized for a reason other than COVID-19 but who otherwise meet the EUA criteria.

The Panel's statement includes a detailed discussion of the rationale for these recommendations.

The COVID-19 Treatment Guidelines Panel’s Statement on the Emergency Use Authorization of Anti-SARS-CoV-2 Monoclonal Antibodies for the Treatment of COVID-19

Last Updated: April 8, 2021

Anti-SARS-CoV-2 monoclonal antibodies that target the SARS-CoV-2 spike protein and block virus entry into cells have been evaluated for the treatment of COVID-19. To date, the Food and Drug Administration (FDA) has issued Emergency Use Authorizations (EUAs) for the following anti-SARS-CoV-2 monoclonal antibodies and combinations: bamlanivimab alone, bamlanivimab plus etesevimab, and casirivimab plus imdevimab.

Data are emerging on the currently available anti-SARS-CoV-2 monoclonal antibodies, including preliminary data from a Phase 3 trial of casirivimab plus imdevimab, and on the in vitro susceptibility of SARS-CoV-2 variants to anti-SARS-CoV-2 monoclonal antibodies. After reviewing the available data, the COVID-19 Treatment Guidelines Panel (the Panel) has updated its recommendations on the use of anti-SARS-CoV-2 monoclonal antibodies in outpatients with mild to moderate COVID-19 who are at high risk of disease progression. In addition, the Panel notes that, because of an increasing number of reports of variants that are resistant to bamlanivimab alone, this product will no longer be distributed by the U.S. government.¹

Summary Recommendations and Considerations

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using one of the following combination anti-SARS-CoV-2 monoclonal antibodies to treat outpatients with mild to moderate COVID-19 who are at high risk of clinical progression, as defined by the Emergency Use Authorization (EUA) criteria (listed in alphabetical order):
 - **Bamlanivimab 700 mg plus etesevimab 1,400 mg (AIIa); or**
 - **Casirivimab 1,200 mg plus imdevimab 1,200 mg (AIIa).**
- Treatment should be started as soon as possible after the patient receives a positive result on a SARS-CoV-2 antigen or nucleic acid amplification test (NAAT) and within 10 days of symptom onset.
- There are no comparative data to determine whether there are differences in clinical efficacy or safety between bamlanivimab plus etesevimab and casirivimab plus imdevimab.
 - There are SARS-CoV-2 variants, particularly those that contain the mutation E484K (see below), that reduce the virus’ susceptibility to bamlanivimab and, to a lesser extent, casirivimab and etesevimab in vitro; however, the clinical impact of these mutations is not known.
 - In regions where SARS-CoV-2 variants with reduced in vitro susceptibility to bamlanivimab plus etesevimab are common, some Panel members would preferentially use casirivimab plus imdevimab while acknowledging that it is not known whether in vitro susceptibility data correlate with clinical outcomes.
- Because clinical outcome data are limited and there are concerns regarding decreased susceptibility of variants, the Panel **recommends against** the use of **bamlanivimab monotherapy (AIII)**.
 - If combination products are not available, the use of bamlanivimab monotherapy can be considered for people who meet the EUA criteria on a case-by-case basis.
- The Panel **recommends against** the use of **anti-SARS-CoV-2 monoclonal antibodies** for patients who are hospitalized because of COVID-19, except in a clinical trial (**AIIa**). However, their use should be considered for persons with mild to moderate COVID-19 who are hospitalized for a reason other than COVID-19 but who otherwise meet the EUA criteria.

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

Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

SARS-CoV-2 Variants of Concern or Interest and Their Susceptibility to Anti-SARS-CoV-2 Monoclonal Antibodies

In laboratory studies, some SARS-CoV-2 variants of concern or interest that harbor certain mutations have markedly reduced susceptibility to bamlanivimab and may have lower sensitivity to etesevimab and casirivimab. However, the impact of these mutations on the clinical response to antibody combinations is uncertain, and the prevalence of these variants in different regions may vary.² Of note:

- The B.1.1.7 variant of concern, which is increasing in frequency in the United States, retains in vitro susceptibility to the anti-SARS-CoV-2 monoclonal antibodies that are currently available through EUAs.³⁻⁵
- The B.1.351 variant of concern has been infrequently detected among the SARS-CoV-2 samples sequenced in the United States to date. This variant includes the E484K mutation, which results in a marked reduction in in vitro susceptibility to bamlanivimab.^{4,6,7} In vitro studies suggest that bamlanivimab plus etesevimab has markedly reduced activity against the B.1.351 variant.³ In vitro studies also suggest that the K417N mutation, which is present in this variant along with the E484K mutation, reduces casirivimab activity, although the combination of casirivimab and imdevimab appears to retain activity.⁵
- The P.1 variant of concern has been infrequently detected among the SARS-CoV-2 samples sequenced in the United States to date. This variant includes the E484K mutation, which results in a marked reduction in in vitro susceptibility to bamlanivimab.^{3,7} In vitro studies suggest that bamlanivimab plus etesevimab also has markedly reduced activity against the P.1 variant.^{3,6,8} In vitro studies also suggest that the K417T mutation, which is present in this variant along with the E484K mutation, reduces casirivimab activity, although the combination of casirivimab and imdevimab appears to retain activity.⁵
- The B.1.429/B.1.427 variants of concern (also called 20C/CAL.20C) that are circulating in parts of the United States, including California, Arizona, and Nevada, have the L452R mutation. This mutation is associated with a marked reduction in in vitro susceptibility to bamlanivimab. There appears to be a modest in vitro decrease in susceptibility to the combination of bamlanivimab and etesevimab, although the clinical implications of this finding are not known.³
- The B.1.526 variant of interest is circulating in parts of the United States, such as New York. It commonly has the E484K mutation, which is associated with a marked reduction in in vitro susceptibility to bamlanivimab.³ There appears to also be reduced in vitro susceptibility to the combination of bamlanivimab and etesevimab, although the clinical implications of this finding are not known.³ In vitro studies suggest that the E484K mutation may reduce casirivimab activity, although the combination of casirivimab and imdevimab appears to retain activity.⁵

Ongoing [population-based genomic surveillance](#) of the types and frequencies of circulating SARS-CoV-2 variants and studies on the susceptibility of different variants to available anti-SARS-CoV-2 monoclonal antibodies will be important in defining the utility of specific monoclonal antibodies in the future.

Rationale for Recommending Bamlanivimab Plus Etesevimab

In the Phase 3 Blocking Viral Attachment and Cell Entry with SARS-CoV-2 Neutralizing Antibodies (BLAZE-1) trial, all the participants met the criteria for being at high risk for progressing to severe COVID-19 and/or hospitalization (as defined in the EUA). A total of 1,035 participants were randomized to receive bamlanivimab 2,800 mg plus etesevimab 2,800 mg (n = 518) or placebo (n = 517).

The median participant age at baseline was 56 years; 31% of the participants were aged ≥ 65 years.

Across the arms, 52% of the participants were women, 87% were White, 29% were Hispanic/Latinx, and 8% were Black or African American. The mean duration of symptoms at study enrollment was 4 days, and 77% of the participants had mild COVID-19.

The primary endpoint was the proportion of participants who had a COVID-19-related hospitalization (defined as ≥ 24 hours of acute care) or who died from any cause by Day 29. Endpoint events occurred in 11 of 518 participants (2%) in the bamlanivimab plus etesevimab arm and in 36 of 517 participants (7%) in the placebo arm. Compared to the placebo-treated participants, the participants who received bamlanivimab plus etesevimab had a 5% absolute reduction and a 70% relative reduction in COVID-19-related hospitalizations or death from any cause ($P < 0.001$). There were no deaths in the bamlanivimab plus etesevimab arm, and 10 deaths occurred in the placebo arm (10 of 517 participants [2%] died; $P < 0.001$).

Secondary virologic endpoints included SARS-CoV-2 levels on nasopharyngeal (NP) swab assays at different time points. Study participants who received bamlanivimab plus etesevimab had a greater and more rapid decline in virus levels than those who received placebo. The proportion of participants with persistently high viral loads (defined as a SARS-CoV-2 level $> 5.27 \log_{10}$ copies/mL at Day 7) was 10% in the bamlanivimab plus etesevimab arm and 29% in the placebo arm ($P < 0.000001$).

Recommendations for the use of bamlanivimab plus etesevimab should be considered in the context of the following limitations:

- The doses authorized in the EUA are bamlanivimab 700 mg plus etesevimab 1,400 mg, which are different from the doses of bamlanivimab 2,800 mg plus etesevimab 2,800 mg used in the Phase 3 BLAZE-1 study. The lower dose was authorized by the FDA based on preliminary data from BLAZE-4, a double-blind, placebo-controlled, randomized Phase 2 trial.³ The available data demonstrate that the antiviral activity of bamlanivimab 700 mg plus etesevimab 1,400 mg is similar to that of bamlanivimab 2,800 mg plus etesevimab 2,800 mg.
- The results of the Phase 3 BLAZE-1 trial have not been peer reviewed and published.
- The Panel's recommendations are based on preliminary results only, and the details on the study design, follow-up, and methods are currently limited. When peer-reviewed data for the Phase 3 BLAZE-1 trial become publicly available, the Panel will review the results and update the recommendations if necessary.

Rationale for Recommending Casirivimab Plus Imdevimab

The updated recommendation for the use of casirivimab plus imdevimab is based on Phase 3 results from the [R10933-10987-COV-2067](#) study (the information from this study is currently available only in a press release, and there is currently no peer-reviewed preprint or publication).^{9,10} This trial compared 1,355 participants who received casirivimab 1,200 mg plus imdevimab 1,200 mg to 1,341 participants who received placebo.

The modified full analysis set (mFAS) included participants who had a positive SARS-CoV-2 polymerase chain reaction result from an NP swab at randomization and one or more risk factors for severe COVID-19. In the mFAS cohort:

- The median participant age at baseline was 50 years. Across the arms, 35% of the participants were Hispanic/Latinx and 5% were Black or African American. The median duration of symptoms prior to enrollment was 3 days.
- COVID-19-related hospitalizations or death from any cause were reported in 18 of 1,355 participants (1.3%) in the casirivimab plus imdevimab arm and 62 of 1,341 participants (4.6%)

in the placebo arm ($P < 0.0001$). This represents a 3.3% absolute reduction and a 71% relative reduction in hospitalization or death in the casirivimab plus imdevimab treatment participants.

In the full analysis set, there was 1 death out of 1,849 participants in the casirivimab plus imdevimab arm and 5 deaths out of 1,843 participants in the placebo arm.

Recommendations for casirivimab plus imdevimab should be considered in the context of the following limitations:

- The results of this clinical trial have not been peer reviewed and published.
- The Panel's recommendation is based on preliminary results only, and the details on the study design, follow-up, and methods are limited. When peer-reviewed data for this trial become publicly available, the Panel will review the results and update the recommendations if necessary.

Rationale for Recommending Against the Use of Bamlanivimab Monotherapy

As noted above, several circulating SARS-CoV-2 variants have mutations that are associated with reduced in vitro susceptibility to certain anti-SARS-CoV-2 monoclonal antibodies that are available through EUAs. In laboratory studies, [some SARS-CoV-2 variants of concern or interest](#) that harbor certain mutations have markedly reduced susceptibility to bamlanivimab alone and possibly lower sensitivity to etesevimab and casirivimab. Reduced in vitro susceptibility to both antibodies in a combination regimen is currently uncommon. Because this field is moving quickly, and real-time testing for variants and mutations is not currently available, it seems prudent to use therapeutic options for which reduced susceptibility to the entire regimen is less likely. Therefore, the Panel **recommends against** the use of **bamlanivimab monotherapy (AIII)**. If combination products are not available, the use of bamlanivimab monotherapy can be considered for people who meet the EUA criteria on a case-by-case basis.

Rationale for Recommending Against the Use of Anti-SARS-CoV-2 Monoclonal Antibodies in Patients Who Are Hospitalized for COVID-19

The FDA EUAs do not authorize the use of these antibodies in patients who are hospitalized for COVID-19, although their use could be considered for patients who are hospitalized for a non-COVID-19 indication and who meet the EUA criteria for the use of these products. See [Anti-SARS-CoV-2 Monoclonal Antibodies](#) for further discussion of the clinical trial data for hospitalized patients.

Anti-SARS-CoV-2 monoclonal antibodies may be available through expanded access programs for the treatment of immunocompromised patients who are hospitalized because of COVID-19. It is not yet known whether these antibodies provide clinical benefits in people with B-cell immunodeficiency or other immunodeficiencies.

Vaccination

SARS-CoV-2 vaccination should be deferred for at least 90 days in people who have received anti-SARS-CoV-2 monoclonal antibodies. This is a precautionary measure, as the antibody treatment may interfere with vaccine-induced immune responses.¹¹

For people who develop COVID-19 after receiving SARS-CoV-2 vaccination, prior vaccination should not affect treatment decisions, including the use of and timing of treatment with monoclonal antibodies.¹¹

High-Risk Criteria in the Emergency Use Authorizations for Anti-SARS-CoV-2 Monoclonal Antibodies

The FDA EUAs for all available anti-SARS-CoV-2 monoclonal antibodies and combinations have the same criteria for use: they allow for the use of the monoclonal antibodies for the treatment of COVID-19 in nonhospitalized adults and children aged ≥ 12 years and weighing ≥ 40 kg who are at high risk for progressing to severe COVID-19 and/or hospitalization.³

High-risk individuals as specified in the EUA are those who meet at least one of the following criteria:

- Body mass index (BMI) ≥ 35
- Chronic kidney disease
- Diabetes mellitus
- Immunocompromising condition
- Currently receiving immunosuppressive treatment
- Aged ≥ 65 years
- Aged ≥ 55 years and have:
 - Cardiovascular disease; *or*
 - Hypertension; *or*
 - Chronic obstructive pulmonary disease/other chronic respiratory disease.
- Aged 12 to 17 years and have:
 - BMI ≥ 85 th percentile for their age and gender based on the [Centers for Disease Control and Prevention growth charts](#); *or*
 - Sickle cell disease; *or*
 - Congenital or acquired heart disease; *or*
 - Neurodevelopmental disorders (e.g., cerebral palsy); *or*
 - A medically related technological dependence that is not related to COVID-19 (e.g., tracheostomy, gastrostomy, positive pressure ventilation); *or*
 - Asthma or a reactive airway or other chronic respiratory disease that requires daily medication for control.

References

1. Public Health Emergency. Outpatient monoclonal antibody treatment for COVID-19 made available under emergency use authorization. March 24, 2021, update on COVID-19 variants and impact on bamlanivimab distribution. 2021. Available at: <https://www.phe.gov/emergency/events/COVID19/investigation-MCM/Bamlanivimab/Pages/default.aspx>. Accessed April 5, 2021.
2. Centers for Disease Control and Prevention. SARS-CoV-2 variant classifications and definitions. 2021. Available at: <https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-surveillance/variant-info.html>. Accessed April 5, 2021.
3. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of bamlanivimab and etesevimab. 2021. Available at: <https://www.fda.gov/media/145802/download>.
4. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of bamlanivimab. 2020. Available at: <https://www.fda.gov/media/143603/download>.
5. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of

REGEN-COV (casirivimab with imdevimab). 2020. Available at: <https://www.fda.gov/media/145611/download>.

6. Wang P, Liu L, Iketani S, et al. Increased resistance of SARS-CoV-2 variants B.1.315 and B.1.1.7 to antibody neutralization. *bioRxiv*. 2021;Preprint. Available at: <https://www.biorxiv.org/content/10.1101/2021.01.25.428137v2>.
7. Wang P, Nair MS, Liu L, et al. Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7. *Nature*. 2021;Published online ahead of print. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33684923>.
8. Wang P, Wang M, Yu J, et al. Increased resistance of SARS-CoV-2 variant P.1 to antibody neutralization. *bioRxiv*. 2021;Preprint. Available at: <https://www.biorxiv.org/content/10.1101/2021.03.01.433466v1>.
9. Phase 3 trial shows REGEN-COV (casirivimab with imdevimab) antibody cocktail reduced hospitalization or death by 70% in non-hospitalized COVID-19 patients. News release. Regeneron. March 23, 2021. Available at: <https://investor.regeneron.com/news-releases/news-release-details/phase-3-trial-shows-regen-covtm-casirivimab-imdevimab-antibody>. Accessed April 5, 2021.
10. Regeneron. COV-2067 Phase 3 trial in high-risk outpatients shows that REGEN-COV (2400 mg and 1200 mg IV doses) significantly reduces risk of hospitalization or death while also shortening symptom duration. 2021. Available at: <https://investor.regeneron.com/static-files/6ab24e8d-9733-4d91-8511-76e56b540723>.
11. Centers for Disease Control and Prevention. Interim clinical considerations for use of COVID-19 vaccines currently authorized in the United States. 2021. Available at: <https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html>. Accessed April 7, 2021.

The COVID-19 Treatment Guidelines Panel's Statement on the Use of Tocilizumab for the Treatment of COVID-19

Last Updated: March 5, 2021

Tocilizumab is a recombinant humanized anti-interleukin (IL)-6 receptor monoclonal antibody approved by the Food and Drug Administration (FDA) for the treatment of certain rheumatologic disorders and cytokine release syndrome induced by chimeric antigen receptor T cell (CAR-T cell) therapy. It is hypothesized that modulating the levels of proinflammatory IL-6 or its effects may reduce the duration and/or severity of COVID-19 illness. To date, no IL-6 inhibitor is FDA-approved or authorized for the treatment of COVID-19.

On February 3, 2021, the COVID-19 Treatment Guidelines Panel (the Panel) issued a statement on the use of tocilizumab that included recommendations based on a preliminary report of results from the Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP). Since the statement was issued, the Panel has reviewed published results of REMAP-CAP¹ and the preliminary results of the open-label, pragmatic Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial,² released on February 11, 2021. Based on this review, the Panel has updated its recommendations on the use of tocilizumab in certain populations of patients with COVID-19.

Recommendations
<p>Based on the collective evidence from the Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) and Randomized Evaluation of COVID-19 Therapy (RECOVERY) trials, the COVID-19 Treatment Guidelines Panel (the Panel) has determined the following:</p> <ul style="list-style-type: none">• The Panel recommends the use of tocilizumab^a (single intravenous dose of 8 mg/kg of actual body weight, up to 800 mg) in combination with dexamethasone (6 mg daily for up to 10 days)^b in certain hospitalized patients who are exhibiting rapid respiratory decompensation due to COVID-19.^c The patients included in this population are:<ul style="list-style-type: none">• Recently hospitalized patients^d who have been admitted to the intensive care unit (ICU) within the prior 24 hours and who require invasive mechanical ventilation, noninvasive mechanical ventilation (NIV), or high-flow nasal canula (HFNC) oxygen (>0.4 FiO₂/30 L/min of oxygen flow) (BIIa); <i>or</i>• Recently hospitalized patients^d (not in the ICU) with rapidly increasing oxygen needs who require NIV or HFNC and have significantly increased markers of inflammation (BIIa) (Note: The RECOVERY trial inclusion criterion for inflammation was C-reactive protein [CRP] ≥75 mg/L; see details below).• For hospitalized patients with hypoxemia who require conventional oxygen supplementation, the Panel recommends using one of the following options: remdesivir (BIIa), dexamethasone plus remdesivir (BIII), or dexamethasone alone (BI) (see Therapeutic Management of Adults With COVID-19).• There is insufficient evidence to specify which of these patients would benefit from the addition of tocilizumab. Some Panel members would also give tocilizumab to patients who are exhibiting rapidly increasing oxygen needs while on dexamethasone and have a CRP ≥75 mg/L but who do not yet require NIV or HFNC, as described above.
<p>Rating of Recommendations: A = Strong; B = Moderate; C = Optional</p> <p>Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion</p>

^a Use of tocilizumab **should be avoided** in patients with any of the following: (1) significant immunosuppression, particularly in those with a history of recent use of other biologic immunomodulating drugs; (2) alanine transaminase >5 times the upper limit of normal; (3) high risk for gastrointestinal perforation; (4) an uncontrolled, serious bacterial, fungal, or non-SARS-CoV-2 viral infection; (5) absolute neutrophil count <500 cells/mL; or (6) platelet count <50,000 cells/mL.

^b As an alternative to dexamethasone, corticosteroids at a dose equivalent to dexamethasone 6 mg are acceptable (see [Corticosteroids](#)).

^c Respiratory decompensation should be due to progressive COVID-19 and not due to alternative causes, such as volume overload or asthma exacerbation.

^d For example, within 3 days. Median days of hospitalization until randomization was 1.2 days (IQR 0.8–2.8 days) in REMAP-CAP and 2 days (IQR 1–5 days) in the RECOVERY trial.

Additional Considerations

- Tocilizumab should be given only in combination with dexamethasone (or another corticosteroid at an equivalent dose).
- Some clinicians may assess a patient’s clinical response to dexamethasone first, before deciding whether tocilizumab is needed.
- Although some patients in the REMAP-CAP and RECOVERY trials received a second dose of tocilizumab at the discretion of treating physicians, there are insufficient data to determine which patients, if any, would benefit from an additional dose of the drug.
- Cases of severe and disseminated strongyloidiasis have been reported with the use of tocilizumab and corticosteroids in patients with COVID-19.^{3,4} Prophylactic treatment with ivermectin should be considered for persons who are from areas where strongyloidiasis is endemic.⁵
- Tocilizumab use **should be avoided** in patients who are significantly immunocompromised. The basis for this precaution is that the REMAP-CAP and RECOVERY trials enrolled very few severely immunocompromised patients, and thus the safety of using tocilizumab plus a corticosteroid in such patients is unknown.
- There are insufficient data to recommend either for or against tocilizumab for the treatment of hospitalized children with COVID-19 or multisystem inflammatory syndrome of children (MIS-C). In children, tocilizumab has been used to treat cytokine release syndrome associated with CAR-T cell therapy and systemic and polyarticular juvenile idiopathic arthritis.
- Health systems are encouraged to ensure that an adequate supply of tocilizumab is available for patients who need the drug for FDA-approved indications.

Rationale for the Panel’s Recommendations

The results of the RECOVERY and REMAP-CAP trials provide consistent evidence that tocilizumab, when added to corticosteroid therapy, offers a modest mortality benefit in certain patients with COVID-19 who are severely ill and exhibit rapid clinical deterioration with increasing oxygen needs and a significant inflammatory response to the virus. However, the Panel found it challenging to define the specific population(s) that would benefit from this intervention. See an overview of the clinical trial data on the use of tocilizumab in patients with COVID-19 below.

For patients with severe to critical COVID-19 who are exhibiting rapid respiratory decompensation, the Panel found that the evidence for a benefit of tocilizumab in combination with dexamethasone was strongest for those who recently started high-flow nasal canula (HFNC) oxygen or noninvasive mechanical ventilation (NIV). REMAP-CAP reported a mortality benefit in their overall study population of patients admitted to the ICU within the prior 24 hours who required invasive mechanical ventilation (IMV), NIV, or HFNC. The RECOVERY trial also suggested a mortality benefit of tocilizumab plus dexamethasone in patients requiring NIV or HFNC. However, it was unclear whether there was a benefit of tocilizumab for patients who received IMV >24 hours after ICU admission.

Although several trials reported before REMAP-CAP and RECOVERY did not show a mortality benefit in patients on HFNC, NIV, or IMV, most of these studies were much smaller; enrolled patients who may not have exhibited rapid clinical progression, patients who received oxygen support >24 hours after ICU admission, and patients later in their ICU course of stay; and included only a minority of patients who were receiving corticosteroids. The concomitant use of corticosteroids is likely an important factor

for treatment outcomes, as the RECOVERY trial showed no benefit of tocilizumab in the subset of participants who were not receiving dexamethasone. Overall, these data provide the basis for the Panel's recommendations on the use of tocilizumab with corticosteroids for certain patients who exhibit rapid respiratory decompensation.

For patients with severe COVID-19 on conventional oxygen therapy who are typically admitted to general medical wards, the Panel found that the evidence was insufficient to identify which patients would benefit from adding tocilizumab to treatment with corticosteroids. Specifically, most previous trials with a high proportion of patients receiving conventional oxygen therapy did not show a treatment effect from tocilizumab, though many were under-powered and had low use of corticosteroids.⁶⁻¹⁰ Although a mortality benefit of tocilizumab was observed in the RECOVERY trial, the study did not identify a particular subgroup of hospitalized patients on conventional oxygen therapy who benefited most from the drug. Among 21,550 participants randomized in the RECOVERY platform trial, only 4,116 (19%) of the participants underwent a second randomization to the tocilizumab intervention, suggesting that the study results are generalizable only to a restricted subset of hospitalized patients. The consort diagram for the RECOVERY trial suggests that patients with clinical evidence of progressive COVID-19 were preferentially selected for the tocilizumab study. The lack of clearly defined clinical criteria and the application of an arbitrary C-reactive protein (CRP) threshold to define inflammation and expected heterogeneity of CRP measurements between assays also influenced the Panel's recommendations. The Panel recognizes that there may be some hospitalized patients who are receiving conventional oxygen therapy who may have progressive hypoxemia and significant systemic inflammation. The addition of tocilizumab to their standard treatment may provide modest benefit. Nevertheless, at present, there is insufficient evidence to fully define and clearly characterize subgroups within this patient population.

Clinical Trial Data Among Hospitalized Patients With COVID-19

Initial studies that evaluated the use of tocilizumab for the treatment of COVID-19 produced conflicting results. Many trials were limited by low statistical power, heterogenous study populations with varying degrees of disease severity, and/or a low frequency of concomitant use of corticosteroids, which has become the standard of care for patients with severe or critical COVID-19.^{8,10,11} These trials failed to demonstrate a reduction in mortality within 1 month of tocilizumab treatment. However, two studies conducted prior to the REMAP-CAP and RECOVERY trials did demonstrate a benefit of tocilizumab. A Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients With Severe COVID-19 Pneumonia (COVACTA) found that tocilizumab treatment lowered the incidence or duration of ICU and hospital stays.¹² The Evaluating Minority Patients With Actemra (EMPACTA) showed that tocilizumab treatment lowered the composite rate of mechanical ventilation or death.⁷ The COVACTA trial primarily enrolled participants who were receiving higher than conventional levels of oxygen therapy (more than two-thirds of the participants were receiving HFNC, NIV, or IMV), and EMPACTA had a very high proportion of concurrent corticosteroid use (80% of participants), which suggests that these factors may contribute to the differences in the treatment effect seen in trials reported prior to REMAP-CAP and RECOVERY.

REMAP-CAP and RECOVERY, the two largest, randomized controlled tocilizumab trials, have reported a mortality benefit of tocilizumab in selected populations. REMAP-CAP enrolled a narrowly defined population of critically ill patients requiring respiratory support who were admitted to an ICU and randomized to receive open-label tocilizumab (n = 353) or usual care (n = 402). Participants were enrolled within 24 hours of ICU admission, and within a median of 1.2 days (IQR 0.8–2.8 days) of hospitalization. Corticosteroids were given to 92.7% and 93.9% of the patients in the tocilizumab and usual care arms, respectively. Compared to usual care, tocilizumab use reduced both in-hospital mortality (28% of the tocilizumab recipients vs. 36% of the usual care recipients died) and time to hospital discharge (HR 1.41; 95% credible interval [CrI], 1.18–1.70) and increased the number of organ support-free days (10 days in the tocilizumab arm vs. 0 days in the usual care arm; OR 1.64; 95% CrI, 1.25–2.14).

Limitations of the REMAP-CAP trial include the open-label design of the study, the limited collection of data on adverse events, and the lack of subgroup analyses by oxygen requirement at enrollment.¹

The RECOVERY trial enrolled hospitalized patients with COVID-19 into an open-label, platform trial of several treatment options. A subset of participants with hypoxemia (i.e., SpO₂ <92% or need for supplemental oxygen) and CRP level ≥75 mg/L were offered enrollment into a second randomization (1:1) to tocilizumab (8 mg/kg once, with possible second dose) versus usual care. Across the tocilizumab arm (n = 2,022) and the usual care arm (n = 2,094), the median duration of hospitalization was 2 days, and 82% of the participants were receiving concomitant corticosteroids. At baseline, 45% of the participants were on conventional oxygen, 41% on HFNC or NIV, and 14% on IMV. The study reported that tocilizumab reduced all-cause mortality through 28 days (29% of tocilizumab recipients vs. 33% of usual care recipients died by Day 28; RR 0.86; 95% CI, 0.77–0.96), as well as the median time to being discharged alive (20 days for the tocilizumab recipients vs. >28 days for the usual care recipients). In the subgroup analysis, the mortality benefit was restricted to participants who were also receiving corticosteroids (RR 0.80; 95% CI, 0.70–0.90); no benefit was seen among those receiving tocilizumab without corticosteroids. Limitations of the RECOVERY trial include its open-label design, the broad eligibility criteria for patients who were offered the second randomization to tocilizumab, the fact that a high proportion of those randomized to tocilizumab did not receive the treatment (17%), and the limited collection of data on adverse events. The study has not yet been published in a peer-reviewed journal.²

References

1. REMAP-CAP Investigators, Gordon AC, Mouncey PR, et al. Interleukin-6 receptor antagonists in critically ill patients with COVID-19. *N Engl J Med*. 2021. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33631065>.
2. RECOVERY Collaborative Group, Horby PW, Pessoa-Amorim G, et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): preliminary results of a randomised, controlled, open-label, platform trial. *medRxiv*. 2021;preprint. Available at: <https://www.medrxiv.org/content/10.1101/2021.02.11.21249258v1>.
3. Lier AJ, Tuan JL, Davis MW, et al. Case report: disseminated strongyloidiasis in a patient with COVID-19. *Am J Trop Med Hyg*. 2020. Available at: <https://www.ajtmh.org/docserver/fulltext/10.4269/ajtmh.20-0699/tpmd200699.pdf?expires=1598276702&id=id&accname=guest&checksum=D8AA596942F31C34007E0FE065AF1F5F>.
4. Marchese V, Crosato V, Gulletta M, et al. Strongyloides infection manifested during immunosuppressive therapy for SARS-CoV-2 pneumonia. *Infection*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32910321>.
5. Stauffer WM, Alpern JD, Walker PF. COVID-19 and dexamethasone: a potential strategy to avoid steroid-related strongyloides hyperinfection. *JAMA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32761166>.
6. Veiga VC, Prats J, Farias DLC, et al. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. *BMJ*. 2021;372:n84. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33472855>.
7. Salama C, Han J, Yau L, et al. Tocilizumab in patients hospitalized with COVID-19 pneumonia. *N Engl J Med*. 2021;384(1):20-30. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33332779>.
8. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of tocilizumab in patients hospitalized with COVID-19. *N Engl J Med*. 2020;383(24):2333-2344. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33085857>.
9. Salvarani C, Dolci G, Massari M, et al. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: a randomized clinical trial. *JAMA Intern Med*. 2021;181(1):24-31. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33080005>.
10. Hermine O, Mariette X, Tharaux PL, et al. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: a randomized clinical trial. *JAMA Intern Med*.

2021;181(1):32-40. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33080017>.

11. Gupta S, Wang W, Hayek SS, et al. Association between early treatment with tocilizumab and mortality among critically ill patients with COVID-19. *JAMA Intern Med*. 2021;181(1):41-51. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33080002>.
12. Rosas I, Bräu N, Waters M, et al. Tocilizumab in hospitalized patients with COVID-19 pneumonia. *medRxiv*. 2020. Available at: <https://www.medrxiv.org/content/10.1101/2020.08.27.20183442v2>.

Introduction

Last Updated: February 11, 2021

The COVID-19 Treatment Guidelines have been developed to provide clinicians with guidance on how to care for patients with COVID-19. Because clinical information about the optimal management of COVID-19 is evolving quickly, these Guidelines will be updated frequently as published data and other authoritative information become available.

Panel Composition

Members of the COVID-19 Treatment Guidelines Panel (the Panel) are appointed by the Panel co-chairs based on their clinical experience and expertise in patient management, translational and clinical science, and/or development of treatment guidelines. Panel members include representatives from federal agencies, health care and academic organizations, and professional societies. Federal agencies and professional societies represented on the Panel include:

- American Association of Critical-Care Nurses
- American Association for Respiratory Care
- American College of Chest Physicians
- American College of Emergency Physicians
- American College of Obstetricians and Gynecologists
- American Society of Hematology
- American Thoracic Society
- Biomedical Advanced Research and Development Authority
- Centers for Disease Control and Prevention
- Department of Defense
- Department of Veterans Affairs
- Food and Drug Administration
- Infectious Diseases Society of America
- National Institutes of Health
- Pediatric Infectious Diseases Society
- Society of Critical Care Medicine
- Society of Infectious Diseases Pharmacists

The inclusion of representatives from professional societies does not imply that their societies have endorsed all elements of these Guidelines.

The names, affiliations, and financial disclosures of the Panel members and ex officio members, as well as members of the Guidelines support team, are provided in the [Panel Roster](#) and [Financial Disclosure](#) sections of the Guidelines.

Development of the Guidelines

Each section of the Guidelines is developed by a working group of Panel members with expertise in the area addressed in the section. Each working group is responsible for identifying relevant information and published scientific literature and for conducting a systematic, comprehensive review of that information

and literature. The working groups propose updates to the Guidelines based on the latest published research findings and evolving clinical information.

New Guidelines sections and recommendations are reviewed and voted on by the voting members of the Panel. To be included in the Guidelines, a recommendation statement must be endorsed by a majority of Panel members; this applies to recommendations for treatments, recommendations against treatments, and cases where there are insufficient data to recommend either for or against treatments. Updates to existing sections that do not affect the rated recommendations are approved by Panel co-chairs without a Panel vote. Panel members are required to keep all Panel deliberations and unpublished data considered during the development of the Guidelines confidential.

Method of Synthesizing Data and Formulating Recommendations

The working groups critically review and synthesize the available data to develop recommendations. Aspects of the data that are considered can include, but are not limited to, the source of the data, the type of study (e.g., randomized controlled trial, prospective or retrospective cohort study, case series), the quality and suitability of the methods, the number of participants, and the effect sizes observed.

The recommendations in these Guidelines are based on scientific evidence and expert opinion. Each recommendation includes two ratings: an uppercase letter (**A**, **B**, or **C**) that indicates the strength of the recommendation and a Roman numeral with or without a lowercase letter (**I**, **IIa**, **IIb**, or **III**) that indicates the quality of the evidence that supports the recommendation (see Table 1).

Table 1. Recommendation Rating Scheme

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement	I: One or more randomized trials without major limitations
B: Moderate recommendation for the statement	IIa: Other randomized trials or subgroup analyses of randomized trials
C: Optional recommendation for the statement	IIb: Nonrandomized trials or observational cohort studies
	III: Expert opinion

To develop the recommendations in these Guidelines, the Panel uses data from the rapidly growing body of published research on COVID-19. The Panel also relies heavily on experience with other diseases, supplemented with members’ evolving clinical experience with COVID-19.

In general, the recommendations in these Guidelines fall into the following categories:

- **The Panel recommends using [blank] for the treatment of COVID-19 (rating).** Recommendations in this category are based on evidence from clinical trials or large cohort studies that demonstrate the clinical or virologic efficacy of a therapy in patients with COVID-19, with the potential benefits outweighing the potential risks.
- **There are insufficient data for the Panel to recommend either for or against the use of [blank] for the treatment of COVID-19 (no rating).** This statement is used in cases when there are insufficient data to make a recommendation. In this case, rationale for this statement is outlined in the text.
- **The Panel recommends against the use of [blank] for the treatment of COVID-19, except in a clinical trial (rating).** This recommendation is used for an intervention that has not clearly demonstrated efficacy in the treatment of COVID-19 and/or has potential safety concerns. More clinical trials are needed to further define the role of the intervention.

- **The Panel recommends against the use of [blank] for the treatment of COVID-19 (rating).**
This recommendation is used in cases when the available data clearly show a safety concern and/or the data show no benefit for the treatment of COVID-19.

Evolving Knowledge on Treatment for COVID-19

Currently, remdesivir, an antiviral agent, is the only Food and Drug Administration-approved drug for the treatment of COVID-19. An array of drugs approved for other indications and multiple investigational agents are being studied for the treatment of COVID-19 in clinical trials around the globe. These trials can be accessed at [ClinicalTrials.gov](https://www.clinicaltrials.gov). In addition, providers can access and prescribe investigational drugs or agents that are approved or licensed for other indications through various mechanisms, including Emergency Use Authorizations (EUAs), Emergency Investigational New Drug (EIND) applications, compassionate use or expanded access programs with drug manufacturers, and/or off-label use.

Whenever possible, the Panel recommends that promising, unapproved, or unlicensed treatments for COVID-19 be studied in well-designed, controlled clinical trials. This recommendation also applies to drugs that have been approved or licensed for indications other than the treatment of COVID-19. The Panel recognizes the critical importance of clinical research in generating evidence to address unanswered questions regarding the safety and efficacy of potential treatments for COVID-19. However, the Panel also realizes that many patients and providers who cannot access these potential treatments via clinical trials still seek guidance about whether to use them.

A large volume of data and publications from randomized controlled trials, observational cohorts, and case series are emerging at a very rapid pace, some in peer-reviewed journals, others as manuscripts that have not yet been peer reviewed, and, in some cases, press releases. The Panel continuously reviews the available data and assesses their scientific rigor and validity. These sources of data and the clinical experiences of the Panel members are used to determine whether new recommendations or changes to the current recommendations are warranted.

Finally, it is important to stress that the rated treatment recommendations in these Guidelines should not be considered mandates. The choice of what to do or not to do for an individual patient is ultimately decided by the patient and their provider.

Overview of COVID-19

Last Updated: December 17, 2020

Epidemiology

The COVID-19 pandemic has exploded since cases were first reported in China in December 2019. As of December 5, 2020, more than 66 million cases of COVID-19—caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection—have been reported globally, including more than 1.5 million deaths.^{1,2}

Individuals of all ages are at risk for infection and severe disease. However, the probability of serious COVID-19 disease is higher in people aged ≥ 60 years, those living in a nursing home or long-term care facility, and those with chronic medical conditions. In an analysis of more than 1.3 million laboratory-confirmed cases that were reported in the United States between January and May 2020, 14% of patients required hospitalization, 2% were admitted to the intensive care unit, and 5% died.³ The percentage of patients who died was 12 times higher (19.5% vs. 1.6%) and the percentage of patients who were hospitalized was six times higher (45.4% vs. 7.6%) in those with reported medical conditions than in those without medical conditions. The mortality rate was highest in those aged >70 years, regardless of the presence of chronic medical conditions. Among those with available data on health conditions, 32% had cardiovascular disease, 30% had diabetes, and 18% had chronic lung disease. Other conditions that may lead to a high risk for severe COVID-19 include cancer, kidney disease, obesity, sickle cell disease, and other immunocompromising conditions. Transplant recipients and pregnant people are also at a higher risk of severe COVID-19.^{2,4-10}

Emerging data from the United States suggest that racial and ethnic minorities experience higher rates of COVID-19 and subsequent hospitalization and death.¹¹⁻¹⁵ However, surveillance data that include race and ethnicity are not available for most reported cases of COVID-19 in the United States.^{2,16} Factors that contribute to the increased burden of COVID-19 in these populations may include over-representation in work environments that confer higher risks of exposure to COVID-19, economic inequality (which limits people's ability to protect themselves against COVID-19 exposure), neighborhood disadvantage,¹⁷ and a lack of access to health care.¹⁶ Structural inequalities in society contribute to health disparities for racial and ethnic minority groups, including higher rates of comorbid conditions (e.g., cardiac disease, diabetes, hypertension, obesity, pulmonary diseases), which further increases the risk of developing severe COVID-19.¹⁵

Clinical Presentation

The estimated incubation period for COVID-19 is up to 14 days from the time of exposure, with a median incubation period of 4 to 5 days.^{6,18,19} The spectrum of illness can range from asymptomatic infection to severe pneumonia with acute respiratory distress syndrome (ARDS) and death. Among 72,314 persons with COVID-19 in China, 81% of cases were reported to be mild (defined in this study as no pneumonia or mild pneumonia), 14% were severe (defined as dyspnea, respiratory frequency ≥ 30 breaths/min, saturation of oxygen [SpO_2] $\leq 93\%$, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen [PaO_2/FiO_2] < 300 mm Hg, and/or lung infiltrates $> 50\%$ within 24 to 48 hours), and 5% were critical (defined as respiratory failure, septic shock, and/or multiorgan dysfunction or failure).²⁰ In a report on more than 370,000 confirmed COVID-19 cases with reported symptoms in the United States, 70% of patients experienced fever, cough, or shortness of breath, 36% had muscle aches, and 34% reported headaches.³ Other reported symptoms have included, but are not limited to, diarrhea, dizziness, rhinorrhea, anosmia, dysgeusia, sore throat, abdominal pain, anorexia, and vomiting.

The abnormalities seen in chest X-rays vary, but bilateral multifocal opacities are the most common. The abnormalities seen in computed tomography of the chest also vary, but the most common are bilateral peripheral ground-glass opacities, with areas of consolidation developing later in the clinical course.²¹ Imaging may be normal early in infection and can be abnormal in the absence of symptoms.²¹

Common laboratory findings in patients with COVID-19 include leukopenia and lymphopenia. Other laboratory abnormalities have included elevated levels of aminotransferase, C-reactive protein, D-dimer, ferritin, and lactate dehydrogenase.

While COVID-19 is primarily a pulmonary disease, emerging data suggest that it also leads to cardiac,^{22,23} dermatologic,²⁴ hematological,²⁵ hepatic,²⁶ neurological,^{27,28} renal,^{29,30} and other complications. Thromboembolic events also occur in patients with COVID-19, with the highest risk occurring in critically ill patients.³¹

The long-term sequelae of COVID-19 survivors are currently unknown. Persistent symptoms after recovery from acute COVID-19 have been described (see [Clinical Spectrum of SARS-CoV-2 Infection](#)). Lastly, SARS-CoV-2 infection has been associated with a potentially severe inflammatory syndrome in children (multisystem inflammatory syndrome in children, or MIS-C).^{32,33} Please see [Special Considerations in Children](#) for more information.

References

1. World Health Organization. Coronavirus disease (COVID-2019) situation reports. 2020. Available at: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/>. Accessed November 25, 2020.
2. Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19): cases in U.S. 2020. Available at: <https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html>. Accessed November 25, 2020.
3. Stokes EK, Zambrano LD, Anderson KN, et al. Coronavirus disease 2019 case surveillance — United States, January 22–May 30, 2020. *MMWR Morb Mortal Wkly Rep*. 2020. Available at: <https://www.cdc.gov/mmwr/volumes/69/wr/pdfs/mm6924e2-H.pdf>.
4. Cai Q, Chen F, Wang T, et al. Obesity and COVID-19 severity in a designated hospital in Shenzhen, China. *Diabetes Care*. 2020;43(7):1392-1398. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32409502>.
5. Garg S, Kim L, Whitaker M, et al. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019 - COVID—NET, 14 states, March 1-30, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(15):458-464. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32298251>.
6. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32109013>.
7. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. 2020;180(7):934-943. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32167524>.
8. Palaiodimos L, Kokkinidis DG, Li W, et al. Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx, New York. *Metabolism*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32422233>.
9. Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19): people who are at increased risk for severe illness. 2020; <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-at-increased-risk.html>. Accessed November 25, 2020.
10. Zambrano LD, Ellington S, Strid P, et al. Update: characteristics of symptomatic women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status—United States, January 22-October 3, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(44):1641-1647. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33151921>.
11. Azar KMJ, Shen Z, Romanelli RJ, et al. Disparities in outcomes among COVID-19 patients in a large health care system in California. *Health Aff (Millwood)*. 2020;39(7):1253-1262. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32437224>.
12. Gold JAW, Wong KK, Szablewski CM, et al. Characteristics and clinical outcomes of adult patients hospitalized with COVID-19—Georgia, March 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(18):545-550. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32379729>.

13. Gross CP, Essien UR, Pasha S, Gross JR, Wang S, Nunez-Smith M. Racial and ethnic disparities in population level COVID-19 mortality. *J Gen Intern Med*. 2020; 35(10): 3097–3099. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7402388>.
14. Nayak A, Islam SJ, Mehta A, et al. Impact of social vulnerability on COVID-19 incidence and outcomes in the United States. *medRxiv*. 2020;Preprint. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32511437>.
15. Price-Haywood EG, Burton J, Fort D, Seoane L. Hospitalization and mortality among black patients and white patients with Covid-19. *N Engl J Med*. 2020;382(26):2534-2543. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32459916>.
16. Centers for Disease Control and Prevention. Health equity considerations and racial and ethnic minority groups. 2020. Available at: <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/racial-ethnic-minorities.html>. Accessed November 25, 2020.
17. Kind AJH, Buckingham WR. Making neighborhood-disadvantage metrics accessible—the neighborhood atlas. *N Engl J Med*. 2018;378(26):2456-2458. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29949490>.
18. Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med*. 2020;382(13):1199-1207. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31995857>.
19. Lauer SA, Grantz KH, Bi Q, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: Estimation and Application. *Ann Intern Med*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32150748>.
20. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72,314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323(13):1239-1242. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32091533>.
21. Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Lancet Infect Dis*. 2020;20(4):425-434. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32105637>.
22. Liu PP, Blet A, Smyth D, Li H. The science underlying COVID-19: implications for the cardiovascular system. *Circulation*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32293910>.
23. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential effects of coronaviruses on the cardiovascular system: a review. *JAMA Cardiol*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32219363>.
24. Sachdeva M, Gianotti R, Shah M, et al. Cutaneous manifestations of COVID-19: report of three cases and a review of literature. *J Dermatol Sci*. 2020;98(2):75-81. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32381430>.
25. Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. *Clin Chem Lab Med*. 2020;58(7):1021-1028. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32286245>.
26. Agarwal A, Chen A, Ravindran N, To C, Thuluvath PJ. Gastrointestinal and liver manifestations of COVID-19. *J Clin Exp Hepatol*. 2020;10(3):263-265. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32405183>.
27. Whittaker A, Anson M, Harky A. Neurological manifestations of COVID-19: a systematic review and current update. *Acta Neurol Scand*. 2020;142(1):14-22. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32412088>.
28. Paniz-Mondolfi A, Bryce C, Grimes Z, et al. Central nervous system involvement by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). *J Med Virol*. 2020;92(7):699-702. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32314810>.
29. Pei G, Zhang Z, Peng J, et al. Renal involvement and early prognosis in patients with COVID-19 pneumonia.

- J Am Soc Nephrol.* 2020;31(6):1157-1165. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32345702>.
30. Su H, Yang M, Wan C, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. *Kidney Int.* 2020;98(1):219-227. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32327202>.
 31. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up. *J Am Coll Cardiol.* 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32311448>.
 32. Chiotos K, Bassiri H, Behrens EM, et al. Multisystem inflammatory syndrome in children during the COVID-19 pandemic: a case series. *J Pediatric Infect Dis Soc.* 2020 13;9(3):393-398. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32463092>.
 33. Belhadjer Z, Meot M, Bajolle F, et al. Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic. *Circulation.* 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32418446>.

Testing for SARS-CoV-2 Infection

Last Updated: February 11, 2021

Summary Recommendations
<ul style="list-style-type: none">• To diagnose acute infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the COVID-19 Treatment Guidelines Panel (the Panel) recommends using a nucleic acid amplification test (NAAT) with a sample collected from the upper respiratory tract (i.e., nasopharyngeal, nasal, or oropharyngeal specimen) (AIII).• For intubated and mechanically ventilated adults who are suspected to have COVID-19 but who do not have a confirmed diagnosis:<ul style="list-style-type: none">• The Panel recommends obtaining lower respiratory tract samples to establish a diagnosis of COVID-19 if an initial upper respiratory tract sample is negative (BII).• The Panel recommends obtaining endotracheal aspirates over bronchial wash or bronchoalveolar lavage samples when collecting lower respiratory tract samples to establish a diagnosis of COVID-19 (BII).• In asymptomatic persons, a NAAT should not be repeated within 90 days of previous SARS-CoV-2 infection, even following a significant exposure to SARS-CoV-2 (AIII).• Because of reports of SARS-CoV-2 reinfection after an initial diagnosis of infection, a NAAT should be considered for persons who have recovered from previous infection and present with symptoms compatible with SARS-CoV-2 infection, in the absence of an alternative diagnosis (BIII).• The Panel recommends against the use of serologic (i.e., antibody) testing as the sole basis for diagnosis of acute SARS-CoV-2 infection (AIII).• The Panel recommends against the use of serologic (i.e., antibody) testing to determine whether a person is immune to SARS-CoV-2 infection (see below for details) (AIII).
Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion

Diagnostic Testing for SARS-CoV-2 Infection

Everyone who has symptoms that are consistent with COVID-19, as well as people with known high-risk exposures to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), should be tested for SARS-CoV-2 infection. Such testing should employ either a nucleic acid amplification test (NAAT) or an antigen test to detect SARS-CoV-2. Ideally, diagnostic testing should also be performed for people who are likely to be at repeated risk of exposure to SARS-CoV-2, such as health care workers and first responders. Testing should also be considered for individuals who spend time in heavily populated environments (e.g., teachers, students, food industry workers) and for travelers. Testing requirements may vary by state, local, and employer policies. Travelers may need evidence of a recent negative test result to enter some states or countries; such documentation may be an acceptable alternative to quarantine upon arrival.

A number of diagnostic tests for SARS-CoV-2 infection (e.g., NAATs, antigen tests) have received emergency use authorizations (EUAs) issued by the Food and Drug Administration (FDA),¹ but no diagnostic test has been approved by the FDA.

Although nasopharyngeal specimens remain the recommended samples for SARS-CoV-2 diagnostic testing, nasal (anterior nares or mid-turbinate) or oropharyngeal swabs are acceptable alternatives.² Lower respiratory tract samples have a higher yield than upper tract samples, but they are often not obtained because of concerns about aerosolization of the virus during sample collection procedures. Some tests that have received EUAs can also be performed on saliva specimens. Testing of other sample types, including stool samples, is currently being studied.

Some tests that have received EUAs allow for self-collection of specimens at home, but these specimens must be sent to a laboratory for processing. In addition, some tests allow for collection and testing of specimens by trained personnel in nonclinical settings, such as in the home or in nursing or assisted living facilities. This allows real-time antigen results to be obtained on site.

Nucleic Acid Amplification Testing for SARS-CoV-2 Infection

Reverse transcriptase polymerase chain reaction (RT-PCR)-based diagnostic tests (which detect viral nucleic acids) are considered the gold standard for detecting current SARS-CoV-2 infection. More recently, NAATs have included a variety of additional platforms (e.g., real-time loop mediated isothermal amplification [RT-LAMP]). Clinically, there may be a window period of up to 5 days after exposure before viral nucleic acids can be detected. However, false negative NAAT results can also occur outside of this 5-day window. Therefore, a single negative test result does not completely exclude SARS-CoV-2 infection in people with a high likelihood of infection based on their exposure history and/or their clinical presentation, and repeat testing using a NAAT should be considered.³

SARS-CoV-2 poses several diagnostic challenges, including potentially discordant shedding of virus from the upper versus the lower respiratory tract. However, due to the high specificity of NAAT, a positive result on a NAAT of an upper respiratory tract sample from a patient with recent onset of SARS-CoV-2-compatible symptoms is sufficient to diagnose COVID-19. In patients with COVID-19, severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS), lower respiratory tract specimens have a higher viral load and thus a higher yield than upper respiratory tract specimens.⁴⁻¹⁰ For intubated or mechanically ventilated patients with clinical signs and symptoms consistent with COVID-19 pneumonia, the COVID-19 Treatment Guidelines Panel (the Panel) recommends obtaining lower respiratory tract samples to establish a diagnosis of COVID-19 if an initial upper respiratory tract sample is negative (**BII**). The Panel recommends obtaining endotracheal aspirates over bronchial wash or bronchoalveolar lavage (BAL) samples when collecting lower respiratory tract samples to establish a diagnosis of COVID-19 (**BII**).

BAL and sputum induction are aerosol-generating procedures that should be performed only after careful consideration of the risk of exposing staff to infectious aerosols. Endotracheal aspiration appears to carry a lower risk of aerosol-generation than BAL, and some experts consider the sensitivity and specificity of endotracheal aspirates and BAL specimens comparable in detecting SARS-CoV-2.

Nucleic Acid Amplification Testing for Individuals With a Previous Positive SARS-CoV-2 Test Result

NAAT can detect SARS-CoV-2 RNA in specimens obtained weeks to months after the onset of COVID-19 symptoms.^{11,12} However, the likelihood of recovering replication-competent virus >10 days from the onset of symptoms in those with mild disease, and >20 days in those with severe disease is very low.^{13,14} Furthermore, both virologic studies and contact tracing of high-risk contacts show a low risk for SARS-CoV-2 transmission after these intervals.^{15,16} On the basis of these results, the [Centers for Disease Control and Prevention \(CDC\)](#) recommends that NAAT should not be repeated in asymptomatic persons within 90 days of previous infection, even following a significant exposure to SARS-CoV-2 (**AIII**).¹⁷ If there are concerns that an immunocompromised health care worker may still be infectious >20 days from the onset of SARS-CoV-2 infection, consultation with local employee health services regarding return-to-work testing policies is advised. Because of reports of SARS-CoV-2 reinfection after an initial diagnosis of SARS-CoV-2 infection, NAAT should be considered in those who have recovered from previous infection and present with compatible symptoms of SARS-CoV-2 infection in the absence of an alternative diagnosis (**BIII**). However, it should be noted that persons infected with SARS-CoV-2 may have a negative result on an initial NAAT and then have a positive result on a subsequent test due

to intermittent detection of viral RNA and not due to reinfection.¹¹ When the results for an initial and a subsequent test are positive, comparative viral sequence data from both tests are needed to distinguish between persistent presence of viral fragments and reinfection. In the absence of viral sequence data, the cycle threshold (Ct) value from a positive NAAT may provide information about whether a newly detected infection is related to the persistence of viral fragments or to reinfection. The Ct value is the number of PCR cycles at which the nucleic acid target in the sample becomes detectable. In general, the Ct value is inversely related to the SARS-CoV-2 viral load. Because the clinical utility of Ct values is an area of active investigation, an expert should be consulted if these values are obtained to guide clinical decisions.

Antigen Testing for SARS-CoV-2 Infection

Antigen-based diagnostic tests (which detect viral antigens) are less sensitive than RT-PCR-based tests, but they have similarly high specificity. Antigen tests perform best early in the course of symptomatic SARS-CoV-2 infection, when the viral load is thought to be highest. Advantages of antigen-based tests are their low cost and rapid turnaround time. The availability of immediate results makes them an attractive option for point-of-care testing in high-risk congregate settings where preventing transmission is critical. Antigen-based tests also allow for repeat testing to quickly identify persons with SARS-CoV-2 infection.

Increasingly, data are available to guide the use of antigen tests as screening tests to detect or exclude SARS-CoV-2 infection in asymptomatic persons, or to determine whether a person who was previously confirmed to have SARS-CoV-2 infection is still infectious. CDC has developed an antigen testing algorithm for persons who have symptoms of COVID-19, persons who are asymptomatic and have a close contact with COVID-19, and persons who are asymptomatic and have no known exposure to a person with COVID-19.¹⁸

The CDC testing algorithm recommends additional NAAT testing when a person who is strongly suspected of having SARS-CoV-2 infection (i.e., symptomatic) receives a negative result, and when a person who is asymptomatic receives a positive result. Antigen tests can yield false positive results for a variety of reasons, including:

- Incomplete adherence to the instructions for antigen test performance, such as reading the results outside the specified time interval or storing test cartridges/cards inappropriately
- Test interference due to human antibodies (e.g., rheumatoid factor or other nonspecific antibodies)
- Use in communities that have a low prevalence of SARS-CoV-2 infection

Serologic or Antibody Testing for Diagnosis of SARS-CoV-2 Infection

Unlike NAATs and antigen tests for SARS-CoV-2 that detect the presence of the virus, serologic or antibody tests can detect recent or prior SARS-CoV-2 infection. Because it may take 21 days or longer after symptom onset for seroconversion (i.e., development of detectable immunoglobulin [Ig] M and/or IgG antibodies to SARS-CoV-2) to occur,¹⁹⁻²⁴ the Panel **does not recommend** serologic testing as the sole basis for diagnosing acute SARS-CoV-2 infection (**AIII**). Because NAATs and antigen tests for SARS-CoV-2 occasionally yield false negative results, serologic tests have been used in some settings as an additional diagnostic test for patients who are strongly suspected to have SARS-CoV-2 infection. Using a serologic test in combination with a NAAT to detect IgG or total antibodies 3 to 4 weeks after symptom onset maximizes the sensitivity and specificity to detect past infection.

No serologic tests for SARS-CoV-2 are approved by the FDA; some, but not all, commercially available serologic tests for SARS-CoV-2 have received EUAs issued by the FDA.¹ Several professional societies

and federal agencies, including the [Infectious Diseases Society of America](#), the [CDC](#), and the [FDA](#), provide guidance on the use of serologic testing for SARS-CoV-2.

Several factors should be considered when using serologic tests for SARS-CoV-2, including:

- Important performance characteristics, including the sensitivity and specificity (i.e., the rates of true positive and true negative results) of many of the commercially available serologic tests, have not been fully characterized. Serologic assays that have FDA EUAs should be used for public health and clinical use. Formal comparisons of serologic tests are in progress.
- Two types of serologic tests have received EUAs from the FDA. The first type are antibody tests that detect the presence of binding antibodies, which bind to a pathogen (e.g., a virus). The second type of tests detect neutralizing antibodies from recent or prior SARS-CoV-2 infection. It is unknown whether one type of test is more clinically meaningful than the other.
- Serologic assays may detect IgM, IgG, IgA, and/or total antibodies, or a combination of IgM and IgG antibodies. Serologic assays that detect IgG and total antibodies have higher specificity to detect past infection than assays that detect IgM and/or IgA antibodies or a combination of IgM and IgG antibodies.
- False positive test results may occur due to cross-reactivity from pre-existing antibodies to other coronaviruses.

Serologic Testing and Immunity to SARS-CoV-2 Infection

The Panel **recommends against** the use of serologic testing to determine whether a person is immune to SARS-CoV-2 infection (**AIII**).

If serologic tests are performed and SARS-CoV-2 antibodies are detected, results should be interpreted with caution for the following reasons:

- It is unclear how long antibodies persist following infection; *and*
- It is unclear whether the presence of antibodies confers protective immunity against future infection.

In communities that have a low prevalence of SARS-CoV-2 infection, the proportion of positive tests that are false positives may be quite high. In these situations, confirmatory testing using a distinct antibody assay, ideally one that uses a different antigenic target (e.g., the nucleocapsid phosphoprotein if the first assay targeted the spike glycoprotein), can substantially improve the probability that persons with positive test results are antibody positive.

Assuming that the test is reliable, serologic tests that identify recent or prior SARS-CoV-2 infection may be used to:

- Differentiate SARS-CoV-2 antibody response to natural infection from vaccine-induced antibody responses to the SARS-CoV-2 spike protein antigen. Because nucleocapsid protein is not a constituent of vaccines currently available under EUA or in late-stage clinical trials, serologic tests that detect antibodies recognizing nucleocapsid protein can be used to distinguish natural infection from vaccine-induced antibody responses.
- Determine who may be eligible to donate convalescent plasma.
- Estimate the proportion of the population exposed to SARS-CoV-2.

Based on current knowledge, serologic tests **should not be used to (AIII)**:

- Make decisions about how to group persons in congregate settings (e.g., schools, dormitories,

correctional facilities)

- Determine whether persons may return to the workplace
- Assess for prior infection solely to determine whether to vaccinate an individual
- Assess for immunity to SARS-CoV-2 following vaccination, except in clinical trials

References

1. Food and Drug Administration. Coronavirus disease 2019 (COVID-19) emergency use authorizations for medical devices. 2020. Available at: <https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations>. Accessed February 4, 2021.
2. Centers for Disease Control and Prevention. Interim guidelines for collecting, handling, and testing clinical specimens from persons for coronavirus disease 2019 (COVID-19). 2020. Available at: <https://www.cdc.gov/coronavirus/2019-ncov/lab/guidelines-clinical-specimens.html>. Accessed February 4, 2021.
3. Kucirka LM, Lauer SA, Laeyendecker O, Boon D, Lessler J. Variation in false-negative rate of reverse transcriptase polymerase chain reaction-based SARS-CoV-2 tests by time since exposure. *Ann Intern Med*. 2020;173(4):262-267. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32422057>.
4. Chan PK, To WK, Ng KC, et al. Laboratory diagnosis of SARS. *Emerg Infect Dis*. 2004;10(5):825-831. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15200815>.
5. Tang P, Louie M, Richardson SE, et al. Interpretation of diagnostic laboratory tests for severe acute respiratory syndrome: the Toronto experience. *CMAJ*. 2004;170(1):47-54. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14707219>.
6. Memish ZA, Al-Tawfiq JA, Makhdoom HQ, et al. Respiratory tract samples, viral load, and genome fraction yield in patients with Middle East respiratory syndrome. *J Infect Dis*. 2014;210(10):1590-1594. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24837403>.
7. Centers for Disease Control and Prevention. Overview of testing for SARS-CoV-2 (COVID-19). 2020. Available at: <https://www.cdc.gov/coronavirus/2019-nCoV/hcp/clinical-criteria.html>. Accessed February 4, 2021.
8. Centers for Disease Control and Prevention. Interim guidelines for collecting, handling, and testing clinical specimens from persons under investigation (PUIs) for Middle East respiratory syndrome coronavirus (MERS-CoV)—Version 2.1. 2019. Available at: <https://www.cdc.gov/coronavirus/mers/guidelines-clinical-specimens.html>. Accessed February 4, 2021.
9. Hase R, Kurita T, Muranaka E, Sasazawa H, Mito H, Yano Y. A case of imported COVID-19 diagnosed by PCR-positive lower respiratory specimen but with PCR-negative throat swabs. *Infect Dis (Lond)*. 2020:1-4. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32238024>.
10. Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in different types of clinical specimens. *JAMA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32159775>.
11. Xiao AT, Tong YX, Zhang S. Profile of RT-PCR for SARS-CoV-2: a preliminary study from 56 COVID-19 patients. *Clin Infect Dis*. 2020;71(16):2249-2251. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32306036>.
12. Rhee C, Kanjilal S, Baker M, Klompas M. Duration of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infectivity: when is it safe to discontinue isolation? *Clin Infect Dis*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33029620>.
13. Arons MM, Hatfield KM, Reddy SC, et al. Presymptomatic SARS-CoV-2 infections and transmission in a skilled nursing facility. *N Engl J Med*. 2020;382(22):2081-2090. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32329971>.

14. Bullard J, Dust K, Funk D, et al. Predicting infectious SARS-CoV-2 from diagnostic samples. *Clin Infect Dis*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32442256>.
15. Cheng HY, Jian SW, Liu DP, et al. Contact tracing assessment of COVID-19 transmission dynamics in Taiwan and risk at different exposure periods before and after symptom onset. *JAMA Intern Med*. 2020;180(9):1156-1163. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32356867>.
16. Korean Disease Control and Prevention Agency. Findings from investigation and analysis of re-positive cases [press release]. 2020. Available at: <https://www.cdc.go.kr/board/board.es?mid=a30402000000&bid=0030>.
17. Centers for Disease Control and Prevention. Duration of isolation and precautions for adults with COVID-19. 2020. Available at: <https://www.cdc.gov/coronavirus/2019-ncov/hcp/duration-isolation.html>. Accessed January 7, 2021.
18. Centers for Disease Control and Prevention. Interim guidance for antigen testing for SARS-CoV-2. 2020. Available at: <https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antigen-tests-guidelines.html>. Accessed January 7, 2021.
19. Guo L, Ren L, Yang S, et al. Profiling early humoral response to diagnose novel coronavirus disease (COVID-19). *Clin Infect Dis*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32198501>.
20. Haveri A, Smura T, Kuivanen S, et al. Serological and molecular findings during SARS-CoV-2 infection: the first case study in Finland, January to February 2020. *Euro Surveill*. 2020;25(11). Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32209163>.
21. Long QX, Liu BZ, Deng HJ, et al. Antibody responses to SARS-CoV-2 in patients with COVID-19. *Nat Med*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32350462>.
22. Okba NMA, Muller MA, Li W, et al. Severe acute respiratory syndrome coronavirus 2-specific antibody responses in coronavirus disease patients. *Emerg Infect Dis*. 2020;26(7):1478-1488. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32267220>.
23. Xiang F, Wang X, He X, et al. Antibody detection and dynamic characteristics in patients with COVID-19. *Clin Infect Dis*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32306047>.
24. Zhao J, Yuan Q, Wang H, et al. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. *Clin Infect Dis*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32221519>.

Prevention and Prophylaxis of SARS-CoV-2 Infection

Last Updated: February 11, 2021

Summary Recommendations
<ul style="list-style-type: none">• The COVID-19 Treatment Guidelines Panel (the Panel) recommends against the use of any drugs for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pre-exposure prophylaxis (PrEP), except in a clinical trial (AIII).• The Panel recommends against the use of hydroxychloroquine for SARS-CoV-2 post-exposure prophylaxis (PEP) (AI).• The Panel recommends against the use of other drugs for SARS-CoV-2 PEP, except in a clinical trial (AIII).• The Panel recommends that health care providers follow recommendations from the Advisory Committee on Immunization Practices when using SARS-CoV-2 vaccines (AI).
Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

General Prevention Measures

Transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is thought to mainly occur through respiratory droplets transmitted from an infectious person to others within six feet of the person. Less commonly, airborne transmission of small droplets and particles of SARS-CoV-2 can occur at distances greater than six feet, and in rare cases, people passing through a room that was previously occupied by an infectious person may become infected. SARS-CoV-2 infection via airborne transmission of small particles tends to occur after prolonged exposure (more than 30 minutes) to an infectious person who is in an enclosed space with poor ventilation.¹

The risk of SARS-CoV-2 transmission can be reduced by covering coughs and sneezes and maintaining a distance of at least six feet from others. When consistent distancing is not possible, face coverings may further reduce the spread of infectious droplets from individuals with SARS-CoV-2 infection to others. Frequent handwashing also effectively reduces the risk of infection.² Health care providers should follow the Centers for Disease Control and Prevention (CDC) recommendations for infection control and appropriate use of personal protective equipment (PPE).³

Vaccines

Currently, no SARS-CoV-2 vaccine has been approved by the Food and Drug Administration (FDA). In December 2020, the FDA issued Emergency Use Authorizations for two mRNA vaccines, BNT162b2 (Pfizer-BioNTech)⁴ and mRNA-1273 (Moderna).⁵ BNT162b2 can be administered to individuals aged ≥ 16 years, whereas mRNA-1273 can be given to individuals aged ≥ 18 years.

In large, placebo-controlled trials, these vaccines were 94% to 95% efficacious in preventing COVID-19 after participants completed a two-dose series. Cases of COVID-19 were confirmed by the presence of symptoms and a positive result on a nucleic acid amplification test (NAAT).^{6,7} Both vaccines also showed efficacy against severe COVID-19. Local and systemic adverse events are relatively common with these vaccines, especially after the second dose; most adverse events were mild or moderate in severity (i.e., they did not prevent recipients from engaging in daily activities). There have been a few reports of severe allergic reactions, including some reports of patients who experienced anaphylaxis after receiving a SARS-CoV-2 mRNA vaccine.⁸ Safety data continue to be collected. Certain populations, such as pregnant and lactating individuals, were not included in the initial vaccine trials. The American College of Obstetricians and Gynecologists has published interim guidance on the use of the SARS-CoV-2 mRNA vaccines in pregnant and lactating people.⁹

It is not known how long SARS-CoV-2 vaccines' protective effect will last or whether SARS-CoV-2 vaccines can prevent asymptomatic infection or transmission, whether they will prevent infection by all current or emergent strains of SARS-CoV-2, whether they will be effective in immunocompromised patients, or whether they will work as well in patients that are at high risk for severe COVID-19 as in those who are at low risk. The efficacy and safety of SARS-CoV-2 vaccines have not been established in children, pregnant people, or immunocompromised patients. Clinical trials for other SARS-CoV-2 vaccine candidates are ongoing.

CDC sets the U.S. adult and childhood immunization schedules based on recommendations from the Advisory Committee on Immunization Practices (ACIP). ACIP considers disease epidemiology, burden of disease, vaccine efficacy and effectiveness, vaccine safety, the quality of the available evidence, and potential implementation issues. ACIP also sets priorities regarding who receives vaccines in the event of a shortage. ACIP COVID-19 vaccine recommendations are reviewed by CDC's Director and, if adopted, are published as official CDC recommendations in the *Morbidity and Mortality Weekly Report*.¹⁰

Pre-Exposure Prophylaxis

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of any drugs for SARS-CoV-2 pre-exposure prophylaxis (PrEP), except in a clinical trial (AIII).

Rationale

At present, there is no known agent that can be administered before exposure to SARS-CoV-2 (i.e., as PrEP) to prevent infection. Clinical trials are investigating several agents, including emtricitabine plus tenofovir alafenamide or tenofovir disoproxil fumarate, hydroxychloroquine, ivermectin, and supplements such as zinc, vitamin C, and vitamin D. Studies of monoclonal antibodies that target SARS-CoV-2 are in development. Please check [ClinicalTrials.gov](https://clinicaltrials.gov) for the latest information.

Clinical Trial Data

Randomized Controlled Trial of Hydroxychloroquine for SARS-CoV-2 Pre-Exposure Prophylaxis Among Health Care Workers

This randomized, double-blind, placebo-controlled trial was designed to determine whether hydroxychloroquine 600 mg per day reduced the frequency of SARS-CoV-2 infection over an 8-week period in hospital-based health care workers. The primary outcome was incidence of SARS-CoV-2 infection as determined by reverse transcriptase polymerase chain reaction (RT-PCR) assay of nasopharyngeal swabs collected at 4 and 8 weeks or the occurrence of COVID-19 symptoms.¹¹

Study Population

- Participants included health care workers at two Philadelphia hospitals who worked ≥ 20 hours per week in a hospital-based unit, had no known history of SARS-CoV-2 infection, and had no COVID-19-like symptoms in the 2 weeks before enrollment. The study enrolled workers in the emergency department and in dedicated COVID-19 treatment units.
- The study excluded individuals who were allergic to hydroxychloroquine and those with glucose-6-phosphate dehydrogenase deficiency, retinal disease, or substantial cardiac disease.

Results

- The study was based on the assumption of a 10% infection rate for the planned inclusion of 100 participants per arm.

- Between April 9 and July 14, 2020, community infection rates declined. At the time of the second interim analysis (when 125 of 132 participants who provided consent were evaluable for the primary endpoint), the Data Safety Monitoring Board recommended early termination of the study for futility.
- Four participants in each group developed SARS-CoV-2 infection (positivity rate of 6.3% vs. 6.6% in the hydroxychloroquine and placebo groups, respectively; $P > 0.99$). Across the groups, six individuals developed symptoms of COVID-19, but none required hospitalization.
- Serologic testing for anti-spike protein immunoglobulin (Ig) M, IgG, and nucleocapsid protein IgG demonstrated more positive results among participants in the hydroxychloroquine group (four participants [7.4%]) than in the placebo group (two participants [3.7%]), although the difference was not statistically significant ($P = 0.40$).
- Mild adverse events were more common among participants in the hydroxychloroquine group than in the placebo group (45% vs. 26%; $P = 0.04$). The greatest difference was the increased frequency of mild diarrhea in the hydroxychloroquine group.
- The rates of treatment discontinuation were similar in the hydroxychloroquine group (19%) and the placebo group (16%).
- There were no cardiac events in either arm and no significant difference in the median frequency of changes in QTc between the study arms ($P = 0.98$).

Limitations

- The study was stopped early.
- Due to the low SARS-CoV-2 infection rate among the participants, the study was underpowered to detect a prophylactic benefit of hydroxychloroquine.
- The study population was mostly young, healthy health care workers; therefore, the applicability of the study findings to other populations is uncertain.

Interpretation

There was no clinical benefit of administering hydroxychloroquine 600 mg per day for 8 weeks as PrEP among health care workers who were exposed to patients with COVID-19. Compared to placebo, hydroxychloroquine was associated with an increased risk of mostly mild adverse events.

Hydroxychloroquine as Pre-Exposure Prophylaxis for COVID-19 in Health Care Workers: a Randomized Trial (COVID PREP Study)

This was a randomized, double-blind, placebo-controlled clinical trial to evaluate whether hydroxychloroquine 400 mg given once- or twice-weekly for 12 weeks (compared to placebo) can prevent SARS-CoV-2 infection in health care workers at high-risk of exposure. The primary outcome was COVID-19-free survival time. Diagnosis of COVID-19 was defined as having laboratory-confirmed SARS-CoV-2 infection or having cough, shortness of breath, or difficulty breathing or having two or more of the following symptoms: fever, chills, rigors, myalgia, headache, sore throat, or new olfactory and taste disorders. COVID-19-compatible illness was included as a primary outcome even if a SARS-CoV-2 PCR test was not performed or if it was performed and the result was negative.¹²

Study Population

- The study participants had to be working in the emergency department, in the intensive care unit, on a dedicated COVID-19 hospital ward, or as a first responder; alternatively, they had to have a job description that included regularly performing aerosol-generating procedures.
- Participants were recruited via social media platforms. Informed consent was obtained remotely,

and the study drug was delivered to the participants by couriers.

Results

- The study was powered based on an anticipated 10% event rate of new symptomatic infections. The investigators determined that the study needed to enroll 1,050 participants per arm to have 80% power. However, it became apparent before the first interim analysis that the study would not meet the enrollment target. As a result, enrollment was stopped without unblinding. The investigators attributed the marked decline in enrollment to the negative reports related to the safety of hydroxychloroquine, including a warning from the FDA.
- Among the 1,483 participants who were randomized, baseline characteristics were similar across the study arms.
- The number of individuals who met the primary endpoint of confirmed or suspected SARS-CoV-2 infection was 39 (7.9%) in the placebo group and 29 (5.9%) in both the once- and twice-weekly hydroxychloroquine groups. Among the 97 participants, only 17 were confirmed to be SARS-CoV-2 PCR positive.
- Compared to placebo, the hazard ratio for the primary endpoint was 0.72 (95% CI, 0.4–1.16; $P = 0.18$) for the once-weekly hydroxychloroquine arm and 0.74 (95% CI, 0.46–1.19; $P = 0.22$) for the twice-weekly hydroxychloroquine arm.
- There were no significant differences for any of the secondary efficacy endpoints among the three groups.
- There were significantly more adverse events reported in the once- and twice-weekly hydroxychloroquine arms (31% vs. 36% of participants experienced adverse events; $P < 0.001$ for both groups) than in the placebo group (21% of participants). The most common side effects were upset stomach and nausea.
- Drug concentrations were measured in dried whole blood samples from a subset of 180 participants who received hydroxychloroquine. The median hydroxychloroquine concentrations for the twice- and once-weekly hydroxychloroquine groups were 200 ng/mL and 98 ng/mL, respectively; both of these concentrations are substantially below the in vitro half-maximal effective concentration (EC_{50}) of hydroxychloroquine. The investigators noted that the simulations that were used to determine the hydroxychloroquine dose for the study predicted much higher drug concentrations than the observed levels.

Limitations

- The study was prematurely halted due to poor enrollment; therefore, the study population was insufficient to detect differences in outcomes among the study arms.
- The study only assessed the SARS-CoV-2 inhibitory activity of two doses of hydroxychloroquine, neither of which achieved concentrations that exceeded the in vitro EC_{50} of the drug.
- Only 17.5% of the participants who met study endpoints had positive SARS-CoV-2 test results; the remainder had compatible symptoms without a confirmatory diagnosis.

Interpretation

Administering hydroxychloroquine 400 mg once- or twice-weekly did not reduce the number of people with documented SARS-CoV-2 infection or symptoms that were compatible with COVID-19 among health care workers who were at a high risk of infection. These findings suggest that hydroxychloroquine was not effective for SARS-CoV-2 PrEP or that the dose used for this indication was suboptimal.

Post-Exposure Prophylaxis

- The Panel **recommends against** the use of **hydroxychloroquine** for SARS-CoV-2 post-exposure prophylaxis (PEP) (AI).
- The Panel **recommends against** the use of other drugs for SARS-CoV-2 PEP, except in a clinical trial (AIII).

Rationale

At present, there are no known agents that have been shown to be efficacious in preventing infection after exposure to SARS-CoV-2 infection (i.e., as PEP). Several randomized controlled trials have evaluated the use of hydroxychloroquine for SARS-CoV-2 PEP.¹³⁻¹⁵ None of these studies have reported any evidence of efficacy, and all showed an increased risk of adverse events among participants who received hydroxychloroquine compared to controls. A number of agents (e.g., anti-SARS-CoV-2 monoclonal antibodies, hyperimmune gammaglobulin, convalescent plasma, ivermectin, interferons, tenofovir with or without emtricitabine, vitamin D) are currently being investigated for SARS-CoV-2 PEP. Please check [ClinicalTrials.gov](https://www.clinicaltrials.gov) for the latest information.

Clinical Trial Data

Both chloroquine and hydroxychloroquine have in vitro activity against severe acute respiratory syndrome-associated coronavirus (SARS-CoV) and SARS-CoV-2.^{16,17} A small cohort study without a control group suggested that hydroxychloroquine might reduce the risk of SARS-CoV-2 transmission to close contacts.¹⁸

Household-Randomized, Double-Blind, Controlled Trial of SARS-CoV-2 Post-Exposure Prophylaxis With Hydroxychloroquine

A household-randomized, double-blind, controlled trial evaluated the use of hydroxychloroquine as PEP to prevent SARS-CoV-2 infection. The study was conducted at seven institutions in the United States between March and August 2020. Participants were recruited using online advertising, social media, and referrals from hospitals, health departments, and those with laboratory-confirmed SARS-CoV-2 infection.¹³

Households were randomized to receive oral hydroxychloroquine 400 mg once daily for 3 days, followed by hydroxychloroquine 200 mg once daily for an additional 11 days, or oral ascorbic acid 500 mg once daily for 3 days, followed by ascorbic acid 250 mg once daily for 11 days. Mid-turbinate nasal swabs were collected daily during the first 14 days, with the primary endpoint being PCR-confirmed SARS-CoV-2 infection during the first 14 days after enrollment in those who were not infected at baseline.

Study Population

- Eligible participants had close contact with an infected person, which included household contacts or other close contacts (82%) or health care workers (18%) who cared for an infected person without wearing appropriate PPE. Participants must have come into contact with an index person who had received a diagnosis of SARS-CoV-2 infection within the past 14 days, and high-risk exposure to the index people must have occurred within the previous 96 hours.
- Enrollment included 829 participants from 671 households; 407 participants (in 337 households) received hydroxychloroquine, and 422 participants (in 334 households) received ascorbic acid.

Results

- A total of 98 SARS-CoV-2 infections were detected during the first 14 days of follow-up, with an

overall cumulative incidence of 14.3% (95% CI, 11.5% to 17%). Fifty-three events occurred in the hydroxychloroquine group, and 45 events occurred in the control group (aHR 1.10; 95% CI, 0.73–1.66; $P > 0.20$)

- In preplanned analyses, hazard ratios were not significantly different within subgroups based on type of contact, time between the most recent contact and the first dose of the study drug, duration of contact, number of contacts enrolled within the household, quarantine status, index case symptoms, or number of adults or children in the household.
- Adverse events that are associated with the use of hydroxychloroquine, including gastrointestinal symptoms and rash, occurred in 112 participants: 66 participants (16.2%) in the hydroxychloroquine group and 46 participants (10.9%) in the control group ($P = 0.026$).

Limitations

- There was an average window of 2 days between the time of the most recent exposure and the time the study drugs were administered, which may have affected the efficacy of hydroxychloroquine if early initiation is important for efficacy.
- The primary analysis excluded approximately 10% of enrolled people who were shown to be infected at baseline.

Interpretation

In this study, hydroxychloroquine was ineffective when used as PEP for SARS-CoV-2 infection. Participants who received hydroxychloroquine had an expected increased risk of adverse events when compared to those who received ascorbic acid.

Randomized, Double-Blind, Controlled Trial of High-Risk or Moderate-Risk Occupational or Household Exposures

This randomized, double-blind, controlled trial included 821 participants who self-enrolled in the study using an internet-based survey. Participants were randomized to receive either hydroxychloroquine 800 mg given once, followed by hydroxychloroquine 600 mg given 6 to 8 hours later, and then hydroxychloroquine 600 mg given once daily for 4 additional days or placebo. Because enrollment was done online, study drugs were sent by overnight mail, resulting in more than 50% of participants initiating the first dose of their assigned treatment 3 to 4 days after exposure to SARS-CoV-2.¹⁵

Study Population

- Participants had a high or moderate risk of occupational exposure (66% of participants) or household exposure (34% of participants) to SARS-CoV-2.
- High-risk exposure was defined as being within six feet of an individual with confirmed SARS-CoV-2 infection for more than 10 minutes while not wearing a face mask or eye shield (87.6% of participants). Moderate-risk exposure was defined as the same distance and duration of exposure while wearing a face mask but no eye shield (12.4% of participants).

Results

- A total of 107 participants developed the primary outcome of symptomatic illness. Illness was confirmed by a positive result on a SARS-CoV-2 molecular test; if testing was not available, participants were considered to have symptomatic illness if they developed a compatible COVID-19-related syndrome based on CDC criteria.
- Due to limited access to molecular diagnostic testing, SARS-CoV-2 infection was confirmed in only 16 of the 107 participants (15%). There was no statistically significant difference in the incidence of the primary outcome (symptomatic illness) between the hydroxychloroquine group

and the placebo group (11.8% vs. 14.3%; $P = 0.35$).

- There were more adverse events in the hydroxychloroquine group (mostly nausea, loose stools, and abdominal discomfort), with no serious adverse reactions or cardiac arrhythmias.

Limitations

- Initiation of therapy was delayed for at least 3 days after exposure to SARS-CoV-2 in most participants.
- Only 15% of participants who reached the primary outcome had SARS-CoV-2 infection confirmed by molecular diagnostics.
- The study population was young (with a median age of 40 years) and consisted of participants who had a relatively low risk of severe COVID-19.

Interpretation

There was no difference in the incidence of observed symptomatic COVID-19 between participants who received hydroxychloroquine 600 mg once daily and those who received placebo. Although hydroxychloroquine 600 mg per day was associated with an increase in the frequency of adverse events, these adverse events were mostly mild.

Cluster-Randomized Trial of High-Risk Exposures in Spain

This open-label, cluster-randomized trial included 2,314 asymptomatic contacts of 672 COVID-19 cases in Spain.¹⁴ Participants who were epidemiologically linked to a PCR-positive COVID-19 case were defined as study clusters (called rings). All contacts in a ring were simultaneously cluster-randomized 1:1 to receive usual care (the control arm) or hydroxychloroquine 800 mg once daily for 1 day followed by hydroxychloroquine 400 mg once daily for 6 days (the intervention arm). Participants were informed of their allocated study arm after being randomized to the intervention or control arm and signing a consent form.

The primary outcome was onset of laboratory-confirmed COVID-19, defined as a positive result on a SARS-CoV-2 PCR test and at least one of the following symptoms: fever, cough, difficulty breathing, myalgia, headache, sore throat, new olfactory and taste disorders, or diarrhea. A secondary outcome was onset of SARS-CoV-2 infection, defined as either a positive SARS-CoV-2 PCR test result or the presence of any of the symptoms compatible with COVID-19. An additional secondary outcome was development of serological positivity at Day 14.

Study Population

- Study participants were health care or nursing home workers (60.3%), household contacts (27.1%), or nursing home residents (12.7%) who were documented to have spent >15 minutes within two meters of a PCR-positive COVID-19 case during the 7 days prior to enrollment.
- The baseline characteristics of the participants were similar between the two study arms, including comorbidities, number of days of exposure to SARS-CoV-2 before enrollment and randomization, and type of contact.

Results

- A total of 138 study participants (6.0%) developed PCR-confirmed, symptomatic SARS-CoV-2 infection, with no statistical difference for this outcome between the control and intervention arms (6.2% vs. 5.7%; risk ratio 0.86; 95% CI, 0.52–1.42).
- There was no statistical difference between the study arms in the incidence of either PCR-confirmed or symptomatically compatible COVID-19, which occurred in 18.2% of participants:

17.8% in the control arm and 18.7% in the intervention arm (risk ratio 1.03; 95% CI, 0.77–1.38).

- There was no statistical difference between the arms in the rate of positivity for SARS-CoV-2 IgM and/or IgG (8.7% in the control arm vs. 14.3% in the intervention arm; risk ratio 1.57; 95% CI, 0.94–2.62).
- There were more adverse events among the hydroxychloroquine-treated participants (56.1%) than among the controls (5.9%), although most of the adverse events were mild. Common adverse events included gastrointestinal events, nervous system disorders, myalgia, fatigue, and malaise. No serious adverse events were attributed to the study drug.

Limitations

- The study lacked a placebo comparator, which could have had an impact on safety reporting.
- Data regarding the extent of the exposure to the index cases was limited.
- For >50% of the study participants, the time from exposure to the index case to randomization was ≥ 4 days.

Interpretation

The hydroxychloroquine regimen used for PEP in this study did not prevent SARS-CoV-2 infection in healthy individuals who were exposed to a PCR-positive case.

References

1. Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19): scientific brief: SARS-CoV-2 and potential airborne transmission. 2020. Available at: <https://www.cdc.gov/coronavirus/2019-ncov/more/scientific-brief-sars-cov-2.html>. Accessed January 26, 2021.
2. Centers for Disease Control and Prevention. COVID-19: how to protect yourself & others. 2020. Available at: <https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html>. Accessed January 26, 2021.
3. Centers for Disease Control and Prevention. Coronavirus Disease 2019 (COVID-19): Infection control guidance for healthcare professionals about coronavirus (COVID-19). 2020. Available at: <https://www.cdc.gov/coronavirus/2019-ncov/hcp/infection-control.html>. Accessed January 26, 2021.
4. Food and Drug Administration. Fact sheet for healthcare providers administering vaccine (vaccination providers): emergency use authorization (EUA) of the Pfizer-BioNTech COVID-19 vaccine to prevent coronavirus disease 2019 (COVID-19). 2020. Available at: <https://www.fda.gov/media/144413/download>. Accessed January 6, 2021.
5. Food and Drug Administration. Fact sheet for healthcare providers administering vaccine (vaccination providers): emergency use authorization (EUA) of the Moderna COVID-19 vaccine to prevent coronavirus disease 2019 (COVID-19). 2020. Available at: <https://www.fda.gov/media/144637/download>. Accessed January 6, 2021.
6. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. *N Engl J Med*. 2020;383(27):2603-2615. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33301246>.
7. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med*. 2020; Published online ahead of print. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33378609>.
8. Centers for Disease Control and Prevention. Interim considerations: preparing for the potential management of anaphylaxis after COVID-19 vaccination. 2020. Available at: <https://www.cdc.gov/vaccines/covid-19/info-by-product/pfizer/anaphylaxis-management.html>. Accessed

January 6, 2021.

9. The American College of Obstetricians and Gynecologists. Practice advisory: vaccinating pregnant and lactating patients against COVID-19. 2020. Available at: <https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2020/12/vaccinating-pregnant-and-lactating-patients-against-covid-19>. Accessed January 6, 2021.
10. Centers for Disease Control and Prevention. Current COVID-19 ACIP vaccine recommendations. 2020. Available at: <https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/covid-19.html>. Accessed January 6, 2021.
11. Abella BS, Jolkovsky EL, Biney BT, et al. Efficacy and safety of hydroxychloroquine vs placebo for pre-exposure SARS-CoV-2 prophylaxis among health care workers: a randomized clinical trial. *JAMA Intern Med*. 2020; Published online ahead of print. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33001138>.
12. Rajasingham R, Bangdiwala AS, Nicol MR, et al. Hydroxychloroquine as pre-exposure prophylaxis for COVID-19 in healthcare workers: a randomized trial. *Clin Infect Dis*. 2020; Published online ahead of print. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33068425>.
13. Barnabas RV, Brown ER, Bershteyn A, et al. Hydroxychloroquine as postexposure prophylaxis to prevent severe acute respiratory syndrome coronavirus 2 infection: a randomized trial. *Ann Intern Med*. 2020; Published online ahead of print. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33284679>.
14. Mitjà O, Corbacho-Monné M, Ubals M, et al. A cluster-randomized trial of hydroxychloroquine for prevention of COVID-19. *N Engl J Med*. 2020. Available at: <https://www.nejm.org/doi/pdf/10.1056/NEJMoa2021801>.
15. Boulware DR, Pullen MF, Bangdiwala AS, et al. A randomized trial of hydroxychloroquine as postexposure prophylaxis for COVID-19. *N Engl J Med*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32492293>.
16. Yao X, Ye F, Zhang M, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Clin Infect Dis*. 2020;71(15):732-739. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32150618>.
17. Vincent MJ, Bergeron E, Benjannet S, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. *Virol J*. 2005;2:69. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16115318>.
18. Lee SH, Son H, Peck KR. Can post-exposure prophylaxis for COVID-19 be considered as an outbreak response strategy in long-term care hospitals? *Int J Antimicrob Agents*. 2020;55(6):105988. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32305587>.

Clinical Spectrum of SARS-CoV-2 Infection

Last Updated: December 17, 2020

Patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can experience a range of clinical manifestations, from no symptoms to critical illness. This section of the Guidelines discusses the clinical presentation of patients according to illness severity.

In general, adults with SARS-CoV-2 infection can be grouped into the following severity of illness categories. However, the criteria for each category may overlap or vary across clinical guidelines and clinical trials, and a patient's clinical status may change over time.

- *Asymptomatic or Presymptomatic Infection:* Individuals who test positive for SARS-CoV-2 using a virologic test (i.e., a nucleic acid amplification test or an antigen test) but who have no symptoms that are consistent with COVID-19.
- *Mild Illness:* Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging.
- *Moderate Illness:* Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have saturation of oxygen (SpO_2) $\geq 94\%$ on room air at sea level.
- *Severe Illness:* Individuals who have $\text{SpO}_2 < 94\%$ on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) < 300 mm Hg, respiratory frequency > 30 breaths/min, or lung infiltrates $> 50\%$.
- *Critical Illness:* Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

Patients with certain underlying comorbidities are at a higher risk of progressing to severe COVID-19. These comorbidities include being 65 years or older; having cardiovascular disease, chronic lung disease, sickle cell disease, diabetes, cancer, obesity, or chronic kidney disease; being pregnant; being a smoker; and being a recipient of transplant or immunosuppressive therapy.¹ Health care providers should monitor such patients closely until clinical recovery is achieved.

The optimal pulmonary imaging technique has not yet been defined for people with symptomatic SARS-CoV-2 infection. Initial evaluation for these patients may include chest X-ray, ultrasound, or, if indicated, computerized tomography. An electrocardiogram should be performed if indicated. Laboratory testing includes a complete blood count with differential and a metabolic profile, including liver and renal function tests. While not part of standard care, measuring the levels of inflammatory markers such as C-reactive protein (CRP), D-dimer, and ferritin may have prognostic value.²⁻⁴

The definitions for the severity of illness categories listed above also apply to pregnant patients. However, the threshold for certain interventions may be different for pregnant patients and nonpregnant patients. For example, oxygen supplementation is recommended for pregnant patients when SpO_2 falls below 95% on room air at sea level to accommodate physiologic changes in oxygen demand during pregnancy and to ensure adequate oxygen delivery to the fetus.⁵ If laboratory parameters are used for monitoring and for interventions, clinicians should be aware that normal physiologic changes during pregnancy can alter several laboratory values. In general, leukocyte cell count increases throughout gestation and delivery and peaks during the immediate postpartum period. This is mainly due to neutrophilia.⁶ D-dimer and CRP levels also increase during pregnancy and are often higher in pregnant patients than nonpregnant patients.⁷ Detailed information on treating COVID-19 in pregnant patients can be found in [Special Considerations in Pregnancy](#) and in the pregnancy considerations subsection of each

individual section of the Guidelines.

In pediatric patients, radiographic abnormalities are common and, for the most part, should not be the only criteria used to determine the severity of illness category. The normal values for respiratory rate also vary with age in children; thus, hypoxia should be the primary criterion used to define severe illness, especially in younger children. In a small number of children and in some young adults, SARS-CoV-2 infection may be followed by a severe inflammatory condition called multisystem inflammatory syndrome in children (MIS-C).^{8,9} This syndrome is discussed in detail in [Special Considerations in Children](#).

Asymptomatic or Presymptomatic Infection

Asymptomatic SARS-CoV-2 infection can occur, although the percentage of patients who remain truly asymptomatic throughout the course of infection is variable and incompletely defined. It is unclear what percentage of individuals who present with asymptomatic infection progress to clinical disease. Some asymptomatic individuals have been reported to have objective radiographic findings that are consistent with COVID-19 pneumonia.^{10,11} The availability of widespread virologic testing for SARS-CoV-2 and the development of reliable serologic assays for antibodies to the virus will help determine the true prevalence of asymptomatic and presymptomatic infection. See [Therapeutic Management of Patients With COVID-19](#) for recommendations regarding SARS-CoV-2–specific therapy.

Mild Illness

Patients with mild illness may exhibit a variety of signs and symptoms (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell). They do not have shortness of breath, dyspnea on exertion, or abnormal imaging. Most mildly ill patients can be managed in an ambulatory setting or at home through telemedicine or telephone visits. No imaging or specific laboratory evaluations are routinely indicated in otherwise healthy patients with mild COVID-19. Older patients and those with underlying comorbidities are at higher risk of disease progression; therefore, health care providers should monitor these patients closely until clinical recovery is achieved. See [Therapeutic Management of Patients With COVID-19](#) for recommendations regarding SARS-CoV-2–specific therapy.

Moderate Illness

Moderate illness is defined as evidence of lower respiratory disease during clinical assessment or imaging, with $\text{SpO}_2 \geq 94\%$ on room air at sea level. Given that pulmonary disease can progress rapidly in patients with COVID-19, patients with moderate disease should be closely monitored. If bacterial pneumonia or sepsis is suspected, administer empiric antibiotic treatment, re-evaluate the patient daily, and de-escalate or stop antibiotics if there is no evidence of bacterial infection. See [Therapeutic Management of Patients With COVID-19](#) for recommendations regarding SARS-CoV-2–specific therapy.

Severe Illness

Patients with COVID-19 are considered to have severe illness if they have $\text{SpO}_2 < 94\%$ on room air at sea level, a respiratory rate of > 30 breaths/min, $\text{PaO}_2/\text{FiO}_2 < 300$ mm Hg, or lung infiltrates $> 50\%$. These patients may experience rapid clinical deterioration. Oxygen therapy should be administered immediately using a nasal cannula or a high-flow oxygen device. See [Therapeutic Management of Patients With COVID-19](#) for recommendations regarding SARS-CoV-2–specific therapy. If secondary bacterial pneumonia or sepsis is suspected, administer empiric antibiotics, re-evaluate the patient daily, and de-escalate or stop antibiotics if there is no evidence of bacterial infection.

Critical Illness

Critically ill patients may have acute respiratory distress syndrome, septic shock that may represent virus-induced distributive shock, cardiac dysfunction, elevation in levels of multiple inflammatory cytokines that provoke a cytokine storm, and/or exacerbation of underlying comorbidities. In addition to pulmonary disease, patients with critical illness may also experience cardiac, hepatic, renal, central nervous system, or thrombotic disease.

As with any patient in the intensive care unit (ICU), successful clinical management of a patient with COVID-19 includes treating both the medical condition that initially resulted in ICU admission and other comorbidities and nosocomial complications.

For more information, see [Care of Critically Ill Patients With COVID-19](#).

Persistent Symptoms or Organ Dysfunction After Acute COVID-19

There have been an increasing number of reports of patients who experience persistent symptoms and/or organ dysfunction after acute COVID-19. At this time, there is limited information on the prevalence, duration, underlying causes, and effective management strategies for these lingering signs and symptoms.¹² The nomenclature for this phenomenon is evolving, but it has been referred to as “postacute COVID-19 syndrome” or “long COVID,” and affected patients have been referred to as “long haulers.” The incidence, natural history, and etiology of these symptoms are currently unknown. Currently, there is no case definition for postacute COVID-19 syndrome, and no specific time frame has been established to define late sequelae of COVID-19. However, the Centers for Disease Control and Prevention (CDC) recently proposed defining late sequelae as sequelae that extend beyond 4 weeks after initial infection.^{13,14} Some of the symptoms overlap with the post-intensive care syndrome (PICS) that has been described in patients without COVID-19, but prolonged symptoms and disabilities after COVID-19 have also been reported in patients with milder illness, including outpatients (see [General Considerations](#) for information on PICS).^{15,16}

Common persistent symptoms include fatigue, joint pain, chest pain, palpitations, shortness of breath, cognitive impairment, and worsened quality of life.^{17,18} The CDC conducted a telephone survey of a random sample of 292 adult outpatients who had positive polymerase chain reaction results for SARS-CoV-2. Among the 274 respondents who were symptomatic at the time of testing, 35% reported not having returned to their usual state of health 2 weeks or more after testing; 26% of these patients were aged 18 to 34 years (n = 85), 32% were aged 35 to 49 years (n = 96), and 47% were aged ≥ 50 years (n = 89).¹⁶ An age of ≥ 50 years and the presence of three or more chronic medical conditions were associated with not returning to usual health within 14 to 21 days. Moreover, one in five individuals aged 18 to 34 years who did not have chronic medical conditions had not achieved baseline health when interviewed at a median of 16 days from the testing date.

Persistent symptoms have also been reported in pregnant people.¹⁹ Systematic data on persistent symptoms in children following recovery from the acute phase of COVID-19 are not currently available.²⁰ MIS-C is discussed in [Special Considerations in Children](#).

Fatigue

The prevalence of fatigue among 128 individuals from Ireland who had recovered from the acute phase of COVID-19 was examined using the Chalder Fatigue Scale (CFQ-11). More than half of patients reported persistent fatigue at a median of 10 weeks after initial symptoms first appeared (67 of 128 patients; 52.3%). There was no association between illness severity and fatigue.²¹ A postacute outpatient service developed in Italy reported that 87% of 143 patients surveyed reported persistent symptoms at a

mean of 60 days after symptom onset, with the most common symptom being fatigue (which occurred in 53.1% of these patients).²²

Cardiopulmonary

A study from the United Kingdom reported that among 100 hospitalized patients (32 received care in the ICU and 68 received care in hospital wards only), 72% of the ICU patients and 60% of the ward patients experienced fatigue and breathlessness at 4 to 8 weeks after hospital discharge. The authors suggested that posthospital rehabilitation may be necessary for some of these patients.¹⁷ A retrospective study from China found that pulmonary function (as measured by spirometry) was still impaired 1 month after hospital discharge in 31 of 57 patients (54.4%).²³ In a study from Germany that included 100 patients who had recently recovered from COVID-19, cardiac magnetic resonance imaging (MRI) performed a median of 71 days after diagnosis revealed cardiac involvement in 78% of patients and ongoing myocardial inflammation in 60% of patients.²⁴ A retrospective study from China of 26 patients who had recovered from COVID-19 and who had initially presented with cardiac symptoms found abnormalities on cardiac MRI in 15 patients (58%).²⁵ One should review these data and assess the prevalence of cardiac abnormalities in people with postacute COVID-19 syndrome with caution, however, as the results were likely biased by only including patients with cardiac symptoms.

Neuropsychiatric

Neurologic and psychiatric symptoms have also been reported among patients who have recovered from acute COVID-19. High rates of anxiety and depression have been reported in some patients using self-report scales for psychiatric distress.^{18,26} Younger patients have been reported to experience more psychiatric symptoms than patients aged >60 years.^{17,18} Patients may continue to experience headaches, vision changes, hearing loss, loss of taste or smell, impaired mobility, numbness in extremities, tremors, myalgia, memory loss, cognitive impairment, and mood changes for up to 3 months after diagnosis of COVID-19.^{27,28} One study in the United Kingdom administered cognitive tests to 84,285 participants who had recovered from suspected or confirmed cases of SARS-CoV-2 infection. These participants had worse performances across multiple domains than would be expected for people with the given age and demographic profiles; this effect was observed even among those who had not been hospitalized.²⁹ However, the study authors did not report when the tests were administered in relation to the diagnosis of COVID-19.

More research and more rigorous observational cohort studies are needed to better understand the pathophysiology and clinical course of these postinfection sequelae and to identify management strategies for patients. More information about ongoing studies can be found at [ClinicalTrials.gov](https://clinicaltrials.gov).

References

1. Centers for Disease Control and Prevention. COVID-19 (oronavirus disease): people with certain medical conditions. 2020. Available at <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html>. Accessed December 11, 2020.
2. Tan C, Huang Y, Shi F, et al. C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. *J Med Virol*. 2020;92(7):856-862. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32281668>.
3. Berger JS, Kunichoff D, Adhikari S, et al. Prevalence and outcomes of D-dimer elevation in hospitalized patients with COVID-19. *Arterioscler Thromb Vasc Biol*. 2020;40(10):2539-2547. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32840379>.
4. Casas-Rojo JM, Anton-Santos JM, Millan-Nunez-Cortes J, et al. Clinical characteristics of patients hospitalized with COVID-19 in Spain: results from the SEMI-COVID-19 Registry. *Rev Clin Esp*. 2020;220(8):480-494.

Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32762922>.

5. Society for Maternal-Fetal Medicine. Management considerations for pregnant patients with COVID-19. 2020. Available at: https://s3.amazonaws.com/cdn.smfm.org/media/2336/SMFM_COVID_Management_of_COVID_pos_preg_patients_4-30-20_final.pdf. Accessed December 14, 2020.
6. Abbassi-Ghanavati M, Greer LG, Cunningham FG. Pregnancy and laboratory studies: a reference table for clinicians. *Obstet Gynecol*. 2009;114(6):1326-1331. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19935037>.
7. Anderson BL, Mendez-Figueroa H, Dahlke JD, Raker C, Hillier SL, Cu-Uvin S. Pregnancy-induced changes in immune protection of the genital tract: defining normal. *Am J Obstet Gynecol*. 2013;208(4):321.e1-321.e9. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23313311>.
8. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet*. 2020;395(10237):1607-1608. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32386565>.
9. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet*. 2020;395(10239):1771-1778. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32410760>.
10. Zhang R, Ouyang H, Fu L, et al. CT features of SARS-CoV-2 pneumonia according to clinical presentation: a retrospective analysis of 120 consecutive patients from Wuhan city. *Eur Radiol*. 2020;30(8):4417-4426. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32279115>.
11. Inui S, Fujikawa A, Jitsu M, et al. Chest CT findings in cases from the cruise ship Diamond Princess with coronavirus disease 2019 (COVID-19). *Radiology: Cardiothoracic Imaging*. 2020;2(2). Available at: <https://pubs.rsna.org/doi/10.1148/ryct.2020200110>.
12. Marshall M. The lasting misery of coronavirus long-haulers. *Nature*. 2020;585(7825):339-341. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32929257>.
13. Datta SD, Talwar A, Lee JT. A proposed framework and timeline of the spectrum of disease due to SARS-CoV-2 infection: illness beyond acute infection and public health implications. *JAMA*. 2020;324(22):2251-2252. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33206133>.
14. Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute COVID-19 in primary care. *BMJ*. 2020;370:m3026. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32784198>.
15. Rawal G, Yadav S, Kumar R. Post-intensive care syndrome: an overview. *J Transl Int Med*. 2017;5(2):90-92. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28721340>.
16. Tenforde MW, Kim SS, Lindsell CJ, et al. Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistate health care systems network—United States, March–June 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(30):993-998. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32730238>.
17. Halpin SJ, McIvor C, Whyatt G, et al. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: a cross-sectional evaluation. *J Med Virol*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32729939>.
18. Cai X, Hu X, Ekumi IO, et al. Psychological distress and its correlates among COVID-19 survivors during early convalescence across age groups. *Am J Geriatr Psychiatry*. 2020;28(10):1030-1039. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32753338>.
19. Afshar Y, Gaw SL, Flaherman VJ, et al. Clinical presentation of coronavirus disease 2019 (COVID-19) in pregnant and recently pregnant people. *Obstet Gynecol*. 2020;136(6):1117-1125. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33027186>.
20. Ludvigsson JF. Case report and systematic review suggest that children may experience similar long-term effects to adults after clinical COVID-19. *Acta Paediatr*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33205450>.

21. Townsend L, Dyer AH, Jones K, et al. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. *PLoS One*. 2020;15(11):e0240784. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33166287>.
22. Carfi A, Bernabei R, Landi F, Gemelli Against C-P-ACSG. Persistent symptoms in patients after acute COVID-19. *JAMA*. 2020;324(6):603-605. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32644129>.
23. Huang Y, Tan C, Wu J, et al. Impact of coronavirus disease 2019 on pulmonary function in early convalescence phase. *Respir Res*. 2020;21(1):163. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32600344>.
24. Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2020;5(11):1265-1273. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32730619>.
25. Huang L, Zhao P, Tang D, et al. Cardiac involvement in patients recovered from COVID-2019 identified using magnetic resonance imaging. *JACC Cardiovasc Imaging*. 2020;13(11):2330-2339. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32763118>.
26. Mazza MG, De Lorenzo R, Conte C, et al. Anxiety and depression in COVID-19 survivors: Role of inflammatory and clinical predictors. *Brain Behav Immun*. 2020;89:594-600. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32738287>.
27. Lu Y, Li X, Geng D, et al. Cerebral micro-structural changes in COVID-19 patients—an MRI-based 3-month follow-up study. *EClinicalMedicine*. 2020;25:100484. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32838240>.
28. Heneka MT, Golenbock D, Latz E, Morgan D, Brown R. Immediate and long-term consequences of COVID-19 infections for the development of neurological disease. *Alzheimers Res Ther*. 2020;12(1):69. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32498691>.
29. Hampshire A, Trender W, Chamberlain SR, et al. Cognitive deficits in people who have recovered from COVID-19 relative to controls: an N = 84,285 online study. *medRxiv*. 2020:[Preprint]. Available at: <https://www.medrxiv.org/content/10.1101/2020.10.20.20215863v1>.

Care of Critically Ill Patients With COVID-19

Last Updated: December 17, 2020

Summary Recommendations

Infection Control

- 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)**.
- 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, when available **(AIII)**.
- 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)**.
- 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)**.

Hemodynamics

- For adults with COVID-19 and shock, the Panel recommends using dynamic parameters, skin temperature, capillary refilling time, and/or lactate levels over static parameters to assess fluid responsiveness **(BIIa)**.
- For the acute resuscitation of adults with COVID-19 and shock, the Panel recommends using buffered/balanced crystalloids over unbalanced crystalloids **(BIIa)**.
- For the acute resuscitation of adults with COVID-19 and shock, the Panel **recommends against** the initial use of albumin for resuscitation **(BIIa)**.
- The Panel **recommends against** using hydroxyethyl starches for intravascular volume replacement in patients with sepsis or septic shock **(AIIa)**.
- The Panel recommends norepinephrine as the first-choice vasopressor **(AIIa)**. The Panel recommends adding either vasopressin (up to 0.03 units/min) **(BIIa)** or epinephrine **(CIIb)** to norepinephrine to raise mean arterial pressure to target or adding vasopressin (up to 0.03 units/min) **(CIIa)** to decrease norepinephrine dosage.
- When norepinephrine is available, the Panel **recommends against** using dopamine for patients with COVID-19 and shock **(AIIa)**.
- The Panel **recommends against** using low-dose dopamine for renal protection **(BIIa)**.
- The Panel recommends using dobutamine in patients who show evidence of cardiac dysfunction and persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents **(BIII)**.
- The Panel recommends that all patients who require vasopressors have an arterial catheter placed as soon as practical, if resources are available **(BIII)**.
- For adults with COVID-19 and refractory septic shock who are not receiving corticosteroids to treat their COVID-19, the Panel recommends using low-dose corticosteroid therapy (“shock-reversal”) over no corticosteroid therapy **(BIIa)**.

Oxygenation and Ventilation

- For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy, the Panel recommends high-flow nasal cannula (HFNC) oxygen over noninvasive positive pressure ventilation (NIPPV) **(BIIa)**.
- In the absence of an indication for endotracheal intubation, the Panel recommends a closely monitored trial of NIPPV for adults with COVID-19 and acute hypoxemic respiratory failure and for whom HFNC is not available **(BIIa)**.
- For patients with persistent hypoxemia despite increasing supplemental oxygen requirements in whom endotracheal intubation is not otherwise indicated, the Panel recommends considering a trial of awake prone positioning to

improve oxygenation (**CIIa**).

- The Panel **recommends against** using awake prone positioning as a rescue therapy for refractory hypoxemia to avoid intubation in patients who otherwise meet the indications for intubation and mechanical ventilation (**AIII**).
- If intubation becomes necessary, the procedure should be performed by an experienced practitioner in a controlled setting due to the enhanced risk of severe acute respiratory syndrome coronavirus 2 exposure to health care practitioners during intubation (**AIII**).
- For mechanically ventilated adults with COVID-19 and acute respiratory distress syndrome (ARDS):
 - The Panel recommends using low tidal volume (VT) ventilation (VT 4–8 mL/kg of predicted body weight) over higher VT ventilation (VT >8 mL/kg) (**AIIa**).
 - The Panel recommends targeting plateau pressures of <30 cm H₂O (**AIIa**).
 - The Panel recommends using a conservative fluid strategy over a liberal fluid strategy (**BIIa**).
 - The Panel **recommends against** the routine use of inhaled nitric oxide (**AIIa**).
- For mechanically ventilated adults with COVID-19 and moderate-to-severe ARDS:
 - The Panel recommends using a higher positive end-expiratory pressure (PEEP) strategy over a lower PEEP strategy (**BIIa**).
 - For mechanically ventilated adults with COVID-19 and refractory hypoxemia despite optimized ventilation, the Panel recommends prone ventilation for 12 to 16 hours per day over no prone ventilation (**BIIa**).
- For mechanically ventilated adults with COVID-19 and moderate-to-severe ARDS:
 - The Panel recommends using, as needed, intermittent boluses of neuromuscular blocking agents (NMBA) or continuous NMBA infusion to facilitate protective lung ventilation (**BIIa**).
 - In the event of persistent patient-ventilator dyssynchrony, or in cases where a patient requires ongoing deep sedation, prone ventilation, or persistently high plateau pressures, the Panel recommends using a continuous NMBA infusion for up to 48 hours as long as patient anxiety and pain can be adequately monitored and controlled (**BIII**).
- For mechanically ventilated adults with COVID-19, severe ARDS, and hypoxemia despite optimized ventilation and other rescue strategies:
 - The Panel recommends using recruitment maneuvers rather than not using recruitment maneuvers (**CIIa**).
 - If recruitment maneuvers are used, the Panel **recommends against** using staircase (incremental PEEP) recruitment maneuvers (**AIIa**).
 - The Panel recommends using an inhaled pulmonary vasodilator as a rescue therapy; if no rapid improvement in oxygenation is observed, the treatment should be tapered off (**CIII**).

Acute Kidney Injury and Renal Replacement Therapy

- For critically ill patients with COVID-19 who have acute kidney injury and who develop indications for renal replacement therapy, 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 rather than intermittent hemodialysis (**BIII**).

Pharmacologic Interventions

- In patients with COVID-19 and severe or critical illness, there are insufficient data to recommend empiric broad-spectrum antimicrobial therapy in the absence of another indication.
- If antimicrobials are initiated, the Panel recommends that their use should be reassessed daily in order to minimize the adverse consequences of unnecessary antimicrobial therapy (**AIII**).

Extracorporeal Membrane Oxygenation

- There are insufficient data to recommend either for or against the use of extracorporeal membrane oxygenation in patients with COVID-19 and refractory hypoxemia.

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

Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

General Considerations

Last Updated: February 11, 2021

Severe cases of COVID-19 may be associated with hypoxemic respiratory failure, acute respiratory distress syndrome (ARDS), septic shock, cardiac dysfunction, elevation in multiple inflammatory cytokines, thromboembolic disease, and/or exacerbation of underlying comorbidities. In addition to pulmonary disease, patients with COVID-19 may also experience cardiac, hepatic, renal, and central nervous system disease. Because patients with critical illness are likely to undergo aerosol-generating procedures, they should be placed in airborne infection isolation rooms, when available.

Guidance on diagnostic testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can be found in the [Testing for SARS-CoV-2 Infection](#) section.

Most of the recommendations for the management of critically ill patients with COVID-19 are extrapolated from experience with other causes of sepsis.¹ Currently, there is limited information to suggest that the critical care management of patients with COVID-19 should differ substantially from the management of other critically ill patients; however, special precautions to prevent environmental contamination by SARS-CoV-2 are warranted.

As with any patient in the intensive care unit (ICU), successful clinical management of a patient with COVID-19 includes treating both the medical condition that initially resulted in ICU admission and other comorbidities and nosocomial complications.

Comorbid Conditions

Certain attributes and comorbidities (e.g., older age, cardiovascular disease, diabetes, chronic obstructive pulmonary disease, cancer, renal disease, obesity, sickle cell disease, receipt of a solid organ transplant) are associated with an increased risk of severe illness from COVID-19.²

Bacterial Superinfection of COVID-19-Associated Pneumonia

Limited information exists about the frequency and microbiology of pulmonary coinfections and superinfections in patients with COVID-19, such as hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP). Some studies from China emphasize the lack of bacterial coinfections in patients with COVID-19, while other studies suggest that these patients experience frequent bacterial complications.³⁻⁸ There is appropriate concern about performing pulmonary diagnostic procedures such as bronchoscopy or other airway sampling procedures that require disruption of a closed airway circuit in patients with COVID-19. Thus, while some clinicians do not routinely start empiric broad-spectrum antimicrobial therapy for patients with severe COVID-19 disease, other experienced clinicians routinely use such therapy. However, empiric broad-spectrum antimicrobial therapy is the standard of care for the treatment of shock. Antibiotic stewardship is critical to avoid reflexive or continued courses of antibiotics.

Inflammatory Response Due to COVID-19

Patients with COVID-19 may express increased levels of pro-inflammatory cytokines and anti-inflammatory cytokines, which has previously been referred to as “cytokine release syndrome” or “cytokine storm,” although these are imprecise terms. However, these terms are misnomers because the magnitude of cytokine elevation in patients with COVID-19 is modest compared to that in patients with many other critical illnesses, such as sepsis and ARDS.^{9,10}

Patients with COVID-19 and severe pulmonary involvement are well described to also manifest extrapulmonary disease and to exhibit laboratory markers of acute inflammation. Patients with these manifestations of severe pulmonary disease typically progress to critical illness 10 to 12 days after the

onset of COVID-19 symptoms.

Multisystem Inflammatory Syndrome in Adults

In addition, there are case reports describing patients who had evidence of acute or recent SARS-CoV-2 infection (documented by a nucleic acid amplification test or antigen or antibody testing) with minimal respiratory symptoms, but with laboratory markers of severe inflammation (e.g., elevated C-reactive protein [CRP], ferritin, D-dimer, cardiac enzymes, liver enzymes, and creatinine) and various other symptoms, including fever and shock; and signs of cardiovascular, gastrointestinal, dermatologic, and neurologic disease. This constellation of signs and symptoms has been designated multisystem inflammatory syndrome in adults (MIS-A).¹¹ To date, most adults in whom MIS-A has been described have survived. This syndrome is similar to a syndrome previously described in children ([multisystem inflammatory syndrome in children \[MIS-C\]](#)).

MIS-A is defined by the following criteria:

1. A severe illness requiring hospitalization in an individual aged ≥ 21 years,
2. Current or past infection with SARS-CoV-2,
3. Severe dysfunction in one or more extrapulmonary organ systems,
4. Laboratory evidence of elevated inflammatory markers (e.g., CRP, ferritin, D-dimer, interleukin [IL]-6),
5. Absence of severe respiratory illness, *and*
6. Absence of an alternative unifying diagnosis.¹¹

Because there is no specific diagnostic test for MIS-A, diagnosis of this inflammatory syndrome is one of exclusion after other causes (e.g., septic shock) have been eliminated. Although there are currently no controlled clinical trial data in patients with MIS-A to guide treatment of the syndrome, case reports have described the use of intravenous immunoglobulin, corticosteroids, or anti-IL-6 therapy.

COVID-19-Induced Cardiac Dysfunction, Including Myocarditis

A growing body of literature describes cardiac injury or dysfunction in approximately 20% of patients who are hospitalized with COVID-19.^{4,6,12-15} COVID-19 may be associated with an array of cardiovascular complications, including acute coronary syndrome, myocarditis, arrhythmias, and thromboembolic disease.¹⁶

Thromboembolic Events and COVID-19

Critically ill patients with COVID-19 have been observed to have a prothrombotic state, which is characterized by the elevation of certain biomarkers, and there is an apparent increase in the incidence of venous thromboembolic disease in this population. In some studies, thromboemboli have been diagnosed in patients who received chemical prophylaxis with heparinoids.¹⁷⁻¹⁹ Autopsy studies provide additional evidence of both thromboembolic disease and microvascular thrombosis in patients with COVID-19.²⁰ Some authors have called for routine surveillance of ICU patients for venous thromboembolism.²¹ See the [Antithrombotic Therapy in Patients with COVID-19](#) section for a more detailed discussion.

Renal and Hepatic Dysfunction Due to COVID-19

Although SARS-CoV-2 is primarily a pulmonary pathogen, renal and hepatic dysfunction are consistently described in patients with severe COVID-19.⁴ In one case series of patients with critical disease, >15% of the patients required continuous renal replacement therapy.⁶ See the [Acute Kidney Injury and Renal Replacement Therapy](#) section for a more detailed discussion.

Considerations in Children

Several large epidemiologic studies suggest that rates of ICU admission are substantially lower for children with COVID-19 than for adults with the disease. However, severe disease does occur in children.²²⁻²⁷ The risk factors for severe COVID-19 in children have not yet been established. Data from studies of adults with COVID-19 and extrapolation from data on other pediatric respiratory viruses suggest that children who are severely immunocompromised and those with underlying cardiopulmonary disease may be at higher risk for severe COVID-19.

MIS-C, the postinfectious complication of COVID-19 seen in some children, has been described.^{28,29} Certain symptoms of MIS-C often require ICU-level care, including blood pressure and inotropic support. These symptoms include severe abdominal pain, multisystem inflammation, shock, cardiac dysfunction, and, rarely, coronary artery aneurysm. A minority of children with MIS-C meet the criteria for typical or atypical Kawasaki disease. For details on MIS-C clinical features and the treatments that are being investigated, see the [Special Considerations in Children](#) section.

Interactions Between Drugs Used to Treat COVID-19 and Drugs Used to Treat Comorbidities

All ICU patients should be routinely monitored for drug-drug interactions. The potential for drug-drug interactions between investigational medications or medications used off-label to treat COVID-19 and concurrent drugs should be considered.

Sedation Management in Patients With COVID-19

International guidelines provide recommendations on the prevention, detection, and treatment of pain, sedation, and delirium.^{30,31} Sedation management strategies, such as maintaining a light level of sedation (when appropriate) and minimizing sedative exposure, have shortened the duration of mechanical ventilation and the length of stay in the ICU for patients without COVID-19.^{32,33}

The Society of Critical Care Medicine's (SCCM's) ICU Liberation Campaign promotes the ICU Liberation Bundle (A-F) to improve post-ICU patient outcomes. The A-F Bundle includes the following elements:

- A. Assess, prevent, and manage pain;
- B. Both spontaneous awakening and breathing trials;
- C. Choice of analgesia and sedation;
- D. Delirium: assess, prevent, and manage;
- E. Early mobility and exercise; *and*
- F. Family engagement and empowerment.

The A-F Bundle also provides frontline staff with practical application strategies for each element.³⁴ The A-F Bundle should be incorporated using an interprofessional team model. This approach helps standardize communication among team members, improves survival, and reduces long-term cognitive dysfunction of patients.³⁵ Despite the known benefits of the A-F Bundle, its impact has not been directly assessed in patients with COVID-19; however, the use of the Bundle should be encouraged, when appropriate, to improve ICU patient outcomes. Prolonged mechanical ventilation of COVID-19 patients, coupled with deep sedation and potentially neuromuscular blockade, increases the workload of ICU staff. Additionally, significant drug shortages may force clinicians to use older sedatives with prolonged durations of action and active metabolites, impeding routine implementation of the [PADIS Guidelines](#). This puts patients at additional risk for ICU and post-ICU complications.

Post-Intensive Care Syndrome

Patients with COVID-19 are reported to experience prolonged delirium and/or encephalopathy associated with mechanical ventilation.³⁶ Neurological complications are associated with older age and underlying conditions, such as hypertension and diabetes mellitus.³⁷ Autopsy studies have reported both macrovascular and microvascular thrombosis, with evidence of hypoxic ischemia.³⁸ Adequate management requires careful attention to best sedation practices and vigilance in stroke detection.

Post-intensive care syndrome (PICS) is a spectrum of cognitive, psychiatric, and/or physical disability that affects survivors of critical illness and persists after a patient leaves the ICU.³⁹ Patients with PICS may present with varying levels of impairment; including profound muscle weakness (ICU-acquired weakness); problems with thinking and judgment (cognitive dysfunction); and mental health problems, such as problems sleeping, post-traumatic stress disorder (PTSD), depression, and anxiety. ICU-acquired weakness affects 33% of all patients who receive mechanical ventilation, 50% of patients with sepsis, and ≤50% of patients who remain in the ICU for ≥1 week.⁴⁰⁻⁴² Cognitive dysfunction affects 30% to 80% of patients discharged from the ICU.⁴³⁻⁴⁵ About 50% of ICU survivors do not return to work within 1 year after discharge.⁴⁶ Although no single risk factor has been associated with PICS, there are opportunities to minimize the risk of PICS through medication management (using the A-F Bundle), physical rehabilitation, follow-up clinics, family support, and improved education about the syndrome. PICS also affects family members who participate in the care of their loved ones. In one study, a third of family members who had main decision-making roles experienced mental health problems, such as depression, anxiety, and PTSD.⁴⁷

Early reports suggest that some patients with COVID-19 who have been treated in the ICU express manifestations of PICS.⁴⁸ Although specific therapies for COVID-19-induced PICS are not yet available, physicians should maintain a high index of suspicion for cognitive impairment and other related problems in survivors of severe or critical COVID-19 illness.

Other Intensive Care Unit-Related Complications

Patients who are critically ill with COVID-19 are at risk for nosocomial infections and other complications of critical illness care, such as VAP, HAP, catheter-related bloodstream infections, and venous thromboembolism. When treating patients with COVID-19, clinicians also need to minimize the risk of conventional ICU complications to optimize the likelihood of a successful ICU outcome.

Advance Care Planning and Goals of Care

The advance care plans and the goals of care for all critically ill patients must be assessed at hospital admission and regularly thereafter. This is an essential element of care for all patients. Information on palliative care for patients with COVID-19 can be found at the [National Coalition for Hospice and Palliative Care website](#).

To guide shared decision-making in cases of serious illness, advance care planning should include identifying existing advance directives that outline a patient's preferences and values. Values and care preferences should be discussed, documented, and revisited regularly for patients with or without prior directives. Specialty palliative care teams can facilitate communication between clinicians and surrogate decision makers, support frontline clinicians, and provide direct patient care services when needed.

Surrogate decision makers should be identified for all critically ill patients with COVID-19 at hospital admission. Infection-control policies for COVID-19 often create communication barriers for surrogate decision makers, and most surrogates will not be physically present when discussing treatment options with clinicians. Many decision-making discussions will occur via telecommunication.

Acknowledgments

The Surviving Sepsis Campaign (SSC), an initiative supported by the SCCM and the European Society of Intensive Care Medicine, issued *Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19)* in March 2020.¹ The COVID-19 Treatment Guidelines Panel (the Panel) has based the recommendations in this section on the SSC COVID-19 Guidelines with permission, and the Panel gratefully acknowledges the work of the SSC COVID-19 Guidelines Panel. The Panel also acknowledges the contributions and expertise of Andrew Rhodes, MBBS, MD, of St. George’s University Hospitals in London, England, and Waleed Alhazzani, MBBS, MSc, of McMaster University in Hamilton, Canada.

References

1. Alhazzani W, Moller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). *Crit Care Med*. 2020;48(6):e440-e469. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32224769>.
2. Centers for Disease Control and Prevention. Evidence used to update the list of underlying medical conditions that increase a person’s risk of severe illness from COVID-19. 2020. Available at: <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/evidence-table.html>. Accessed December 8, 2020.
3. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. 2020;180(7):934-943. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32167524>.
4. Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington state. *JAMA*. 2020;323(16):1612-1614. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32191259>.
5. Bhatraju PK, Ghassemieh BJ, Nichols M, et al. COVID-19 in critically ill patients in the Seattle region—case series. *N Engl J Med*. 2020;382(21):2012-2022. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32227758>.
6. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32105632>.
7. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ*. 2020;368:m1091. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32217556>.
8. Du Y, Tu L, Zhu P, et al. Clinical features of 85 fatal cases of COVID-19 from Wuhan: a retrospective observational study. *Am J Respir Crit Care Med*. 2020;201(11):1372-1379. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32242738>.
9. Leisman DE, Ronner L, Pinotti R, et al. Cytokine elevation in severe and critical COVID-19: a rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes. *Lancet Respir Med*. 2020;8(12):1233-1244. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33075298>.
10. Sinha P, Matthay MA, Calfee CS. Is a “cytokine storm” relevant to COVID-19? *JAMA Intern Med*. 2020;180(9):1152-1154. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32602883>.
11. Morris SB, Schwartz NG, Patel P, et al. Case series of multisystem inflammatory syndrome in adults associated with SARS-CoV-2 infection—United Kingdom and United States, March–August 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(40):1450-1456. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33031361>.
12. Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol*. 2020;5(7):802-810. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32211816>.
13. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31986264>.
14. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in

- Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32171076>.
15. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061-1069. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32031570>.
 16. Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. *Nat Rev Cardiol*. 2020;17(9):543-558. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32690910>.
 17. Llitjos JF, Leclerc M, Chochois C, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. *J Thromb Haemost*. 2020;18(7):1743-1746. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32320517>.
 18. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med*. 2020;46(6):1089-1098. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32367170>.
 19. Klok FA, Kruip M, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32291094>.
 20. Menter T, Haslbauer JD, Nienhold R, et al. Postmortem examination of COVID-19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings in lungs and other organs suggesting vascular dysfunction. *Histopathology*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32364264>.
 21. Tavazzi G, Civardi L, Caneva L, Mongodi S, Mojoli F. Thrombotic events in SARS-CoV-2 patients: an urgent call for ultrasound screening. *Intensive Care Med*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32322918>.
 22. Sun D, Li H, Lu XX, et al. Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center's observational study. *World J Pediatr*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32193831>.
 23. Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 Among Children in China. *Pediatrics*. 2020;145(6). Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32179660>.
 24. Centers for Disease Control and Prevention. Coronavirus disease 2019 in children—United States, February 12–April 2, 2020. 2020. Available at: <https://www.cdc.gov/mmwr/volumes/69/wr/mm6914e4.htm>. Accessed January 5, 2021.
 25. Chao JY, Derespina KR, Herold BC, et al. Clinical characteristics and outcomes of hospitalized and critically ill children and adolescents with coronavirus disease 2019 (COVID-19) at a tertiary care medical center in New York City. *J Pediatr*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32407719>.
 26. Zachariah P, Johnson CL, Halabi KC, et al. Epidemiology, clinical features, and disease severity in patients with coronavirus disease 2019 (COVID-19) in a children's hospital in New York City, New York. *JAMA Pediatr*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32492092>.
 27. DeBiasi RL, Song X, Delaney M, et al. Severe COVID-19 in children and young adults in the Washington, DC metropolitan region. *J Pediatr*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32405091>.
 28. Whittaker E, Bamford A, Kenny J, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. *JAMA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32511692>.
 29. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32410760>.
 30. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med*. 2013;41(1):263-306. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23269131>.
 31. Devlin JW, Skrobik Y, Gelinas C, et al. Clinical practice guidelines for the prevention and management of

- pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med*. 2018;46(9):e825-e873. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30113379>.
32. Kress JP, Vinayak AG, Levitt J, et al. Daily sedative interruption in mechanically ventilated patients at risk for coronary artery disease. *Crit Care Med*. 2007;35(2):365-371. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17205005>.
 33. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet*. 2008;371(9607):126-134. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18191684>.
 34. Society of Critical Care Medicine. ICU Liberation Bundle (A-F). Available at: <https://www.sccm.org/ICULiberation/ABCDEF-Bundles>. Accessed January 5, 2021.
 35. Barnes-Daly MA, Phillips G, Ely EW. Improving hospital survival and reducing brain dysfunction at seven California community hospitals: implementing PAD guidelines via the ABCDEF bundle in 6,064 patients. *Crit Care Med*. 2017;45(2):171-178. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27861180>.
 36. Helms J, Kremer S, Merdji H, et al. Neurologic features in severe SARS-CoV-2 infection. *N Engl J Med*. 2020;382(23):2268-2270. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32294339>.
 37. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol*. 2020;77(6):683-690. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32275288>.
 38. Solomon IH, Normandin E, Bhattacharyya S, et al. Neuropathological features of COVID-19. *N Engl J Med*. 2020;383(10):989-992. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32530583>.
 39. Society of Critical Care Medicine. Post-intensive care syndrome. 2013. Available at: <https://www.sccm.org/MyICUCare/THRIVE/Post-intensive-Care-Syndrome>. Accessed September 22, 2020.
 40. Fan E, Dowdy DW, Colantuoni E, et al. Physical complications in acute lung injury survivors: a two-year longitudinal prospective study. *Crit Care Med*. 2014;42(4):849-859. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24247473>.
 41. De Jonghe B, Sharshar T, Lefaucheur JP, et al. Paresis acquired in the intensive care unit: a prospective multicenter study. *JAMA*. 2002;288(22):2859-2867. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12472328>.
 42. Ali NA, O'Brien JM, Jr., Hoffmann SP, et al. Acquired weakness, handgrip strength, and mortality in critically ill patients. *Am J Respir Crit Care Med*. 2008;178(3):261-268. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18511703>.
 43. Pandharipande PP, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. *N Engl J Med*. 2013;369(14):1306-1316. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24088092>.
 44. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA*. 2010;304(16):1787-1794. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20978258>.
 45. Mikkelsen ME, Christie JD, Lanken PN, et al. The adult respiratory distress syndrome cognitive outcomes study: long-term neuropsychological function in survivors of acute lung injury. *Am J Respir Crit Care Med*. 2012;185(12):1307-1315. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22492988>.
 46. Kamdar BB, Sepulveda KA, Chong A, et al. Return to work and lost earnings after acute respiratory distress syndrome: a 5-year prospective, longitudinal study of long-term survivors. *Thorax*. 2018;73(2):125-133. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28918401>.
 47. Azoulay E, Pochard F, Kentish-Barnes N, et al. Risk of post-traumatic stress symptoms in family members of intensive care unit patients. *Am J Respir Crit Care Med*. 2005;171(9):987-994. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15665319>.
 48. Carfi A, Bernabei R, Landi F, Gemelli Against C-P-ACSG. Persistent symptoms in patients after acute COVID-19. *JAMA*. 2020;324(6):603-605. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32644129>.

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 µm) 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 viral diseases, including SARS, that both surgical masks and N95 masks reduce transmission of infection.⁶ Current evidence suggests that surgical masks are probably not inferior to N95 respirators for preventing transmission of laboratory-confirmed, seasonal respiratory viral infections (e.g., influenza).^{7,8} A recent systematic review and meta-analysis of randomized controlled trials that compared the protective effect of medical masks with N95 respirators demonstrated that the use of medical masks did not increase laboratory-confirmed viral (including coronavirus) respiratory infection or clinical respiratory illness.⁹

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.^{10,11} 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.

References

1. Yam LY, Chen RC, Zhong NS. SARS: ventilatory and intensive care. *Respirology*. 2003;8 Suppl:S31-35. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15018131>.
2. Twu SJ, Chen TJ, Chen CJ, et al. Control measures for severe acute respiratory syndrome (SARS) in Taiwan. *Emerg Infect Dis*. 2003;9(6):718-720. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12781013>.
3. Centers for Disease Control and Prevention. The National Personal Protective Technology Laboratory (NPPTL): respirator trusted-source information. 2020. Available at: https://www.cdc.gov/niosh/npptl/topics/respirators/disp_part/respsource1quest2.html. Accessed September 23, 2020.
4. Milton DK, Fabian MP, Cowling BJ, Grantham ML, McDevitt JJ. Influenza virus aerosols in human exhaled breath: particle size, culturability, and effect of surgical masks. *PLoS Pathog*. 2013;9(3):e1003205. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23505369>.
5. Qian H, Li Y, Sun H, Nielsen PV, Huang X, Zheng X. Particle removal efficiency of the portable HEPA air cleaner in a simulated hospital ward. *Building Simulation*. 2010;3:215-224. Available at: <https://link.springer.com/article/10.1007/s12273-010-0005-4>.
6. Offeddu V, Yung CF, Low MSF, Tam CC. Effectiveness of masks and respirators against respiratory infections in healthcare workers: a systematic review and meta-analysis. *Clin Infect Dis*. 2017;65(11):1934-1942. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29140516>.

7. World Health Organization. Infection prevention and control during health care when novel coronavirus (nCoV) infection is suspected. 2020. Available at: [https://www.who.int/publications-detail/infection-prevention-and-control-during-health-care-when-novel-coronavirus-\(ncov\)-infection-is-suspected-20200125](https://www.who.int/publications-detail/infection-prevention-and-control-during-health-care-when-novel-coronavirus-(ncov)-infection-is-suspected-20200125). Accessed April 8, 2020.
8. Centers for Disease Control and Prevention. Interim infection prevention and control recommendations for patients with suspected or confirmed coronavirus disease 2019 (COVID-19) in healthcare settings. 2020. Available at: <https://www.cdc.gov/coronavirus/2019-ncov/infection-control/control-recommendations.html>. Accessed September 28, 2020.
9. Bartoszko JJ, Farooqi MAM, Alhazzani W, Loeb M. Medical masks vs N95 respirators for preventing COVID-19 in healthcare workers: a systematic review and meta-analysis of randomized trials. *Influenza Other Respir Viruses*. 2020;14(4):365-373. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32246890>.
10. Tran K, Cimon K, Severn M, Pessoa-Silva CL, Conly J. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review. *PLoS One*. 2012;7(4):e35797. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22563403>.
11. Lewis SR, Butler AR, Parker J, Cook TM, Schofield-Robinson OJ, Smith AF. Videolaryngoscopy versus direct laryngoscopy for adult patients requiring tracheal intubation: a Cochrane Systematic Review. *Br J Anaesth*. 2017;119(3):369-383. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28969318>.

Hemodynamics

Last Updated: October 9, 2020

Most of the hemodynamic recommendations below are similar to those previously published in the *Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016*. Ultimately, patients with COVID-19 who require fluid resuscitation or hemodynamic management of shock should be treated and managed identically to patients with septic shock.¹

COVID-19 patients who require fluid resuscitation or hemodynamic management of shock should be treated and managed for septic shock in accordance with other published guidelines, with the following exceptions.

Recommendation

- For adults with COVID-19 and shock, the COVID-19 Treatment Guidelines Panel (the Panel) recommends using dynamic parameters, skin temperature, capillary refilling time, and/or lactate levels over static parameters to assess fluid responsiveness (**BIIa**).

Rationale

No direct evidence addresses the optimal resuscitation strategy for patients with COVID-19 and shock. In a systematic review and meta-analysis of 13 non-COVID-19 randomized clinical trials (n = 1,652),² dynamic assessment to guide fluid therapy reduced mortality (risk ratio 0.59; 95% CI, 0.42–0.83), intensive care unit (ICU) length of stay (weighted mean difference -1.16 days; 95% CI, -1.97 to -0.36), and duration of mechanical ventilation (weighted mean difference -2.98 hours; 95% CI, -5.08 to -0.89). Dynamic parameters used in these trials included stroke volume variation (SVV), pulse pressure variation (PPV), and stroke volume change with passive leg raise or fluid challenge. Passive leg raising, followed by PPV and SVV, appears to predict fluid responsiveness with the highest accuracy.³ The static parameters included components of early goal-directed therapy (e.g., central venous pressure, mean arterial pressure).

Resuscitation of non-COVID-19 patients with shock based on serum lactate levels has been summarized in a systematic review and meta-analysis of seven randomized clinical trials (n = 1,301). Compared with central venous oxygen saturation-guided therapy, early lactate clearance-directed therapy was associated with a reduction in mortality (relative ratio 0.68; 95% CI, 0.56–0.82), shorter length of ICU stay (mean difference -1.64 days; 95% CI, -3.23 to -0.05), and shorter duration of mechanical ventilation (mean difference -10.22 hours; 95% CI, -15.94 to -4.50).⁴

Recommendation

- For the acute resuscitation of adults with COVID-19 and shock, the Panel recommends using buffered/balanced crystalloids over unbalanced crystalloids (**BIIa**).

Rationale

A pragmatic randomized trial that compared balanced and unbalanced crystalloids in 15,802 critically ill adults found that the rate of the composite outcome of death, new renal-replacement therapy, or persistent renal dysfunction was lower in the balanced crystalloids group (OR 0.90; 95% CI, 0.82–0.99; $P = 0.04$).⁵ A secondary analysis compared outcomes in a subset of patients with sepsis (n = 1,641). Among the sepsis patients in the balanced crystalloids group, there were fewer deaths (aOR 0.74; 95% CI, 0.59–0.93; $P = 0.01$), as well as fewer days requiring vasopressors and renal replacement therapy.⁶

A subsequent meta-analysis of 21 randomized controlled trials (n = 20,213) that included the pragmatic trial cited above compared balanced crystalloids to 0.9% saline for resuscitation of critically ill adults and children and reported nonsignificant differences in hospital mortality (OR 0.91; 95% CI, 0.83–1.01) and acute kidney injury (OR 0.92; 95% CI, 0.84–1.00).⁷

Recommendation

- For the acute resuscitation of adults with COVID-19 and shock, the Panel **recommends against** the initial use of albumin for resuscitation (**BIIa**).

Rationale

A meta-analysis of 20 non-COVID-19 randomized controlled trials (n = 13,047) that compared the use of albumin or fresh-frozen plasma to crystalloids in critically ill patients found no difference in all-cause mortality,⁸ whereas a meta-analysis of 17 non-COVID-19 randomized controlled trials (n = 1,977) that compared the use of albumin to crystalloids specifically in patients with sepsis observed a reduction in mortality (OR 0.82; 95% CI, 0.67–1.0; *P* = 0.047).⁹ Given the higher cost of albumin and the lack of a definitive clinical benefit, the Panel **recommends against** the routine use of albumin for initial acute resuscitation of patients with COVID-19 and shock.

Additional Recommendations Based on General Principles of Critical Care

- The Panel **recommends against** using hydroxyethyl starches for intravascular volume replacement in patients with sepsis or septic shock (**AIIa**).
- The Panel recommends norepinephrine as the first-choice vasopressor (**AIIa**). The Panel recommends adding either vasopressin (up to 0.03 units/min) (**BIIa**) or epinephrine (**CIIfb**) to norepinephrine to raise mean arterial pressure to target or adding vasopressin (up to 0.03 units/minute) (**CIIfa**) to decrease norepinephrine dosage.
- When norepinephrine is available, the Panel **recommends against** using dopamine for patients with COVID-19 and shock (**AIIa**).
- The Panel **recommends against** using low-dose dopamine for renal protection (**BIIa**).
- The Panel recommends using dobutamine in patients who show evidence of cardiac dysfunction and persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents (**BIII**).
- The Panel recommends that all patients who require vasopressors have an arterial catheter placed as soon as practical, if resources are available (**BIII**).
- For adults with COVID-19 and refractory septic shock who are not receiving corticosteroids to treat their COVID-19, the Panel recommends using low-dose corticosteroid therapy (“shock-reversal”) over no corticosteroid therapy (**BIIa**).
- A typical corticosteroid regimen in septic shock is intravenous hydrocortisone 200 mg per day administered either as an infusion or in intermittent doses. The duration of hydrocortisone therapy is usually a clinical decision.
- Patients who are receiving corticosteroids for COVID-19 are receiving sufficient replacement therapy such that they do not require additional hydrocortisone.

References

1. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. *Crit Care Med*. 2017;45(3):486-552. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/28098591>.

2. Bednarczyk JM, Fridfinnson JA, Kumar A, et al. Incorporating dynamic assessment of fluid responsiveness into goal-directed therapy: a systematic review and meta-analysis. *Crit Care Med*. 2017;45(9):1538-1545. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28817481>.
3. Bentzer P, Griesdale DE, Boyd J, MacLean K, Sirounis D, Ayas NT. Will this hemodynamically unstable patient respond to a bolus of intravenous fluids? *JAMA*. 2016;316(12):1298-1309. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27673307>.
4. Pan J, Peng M, Liao C, Hu X, Wang A, Li X. Relative efficacy and safety of early lactate clearance-guided therapy resuscitation in patients with sepsis: a meta-analysis. *Medicine (Baltimore)*. 2019;98(8):e14453. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30813144>.
5. Semler MW, Self WH, Wanderer JP, et al. Balanced crystalloids versus saline in critically ill adults. *N Engl J Med*. 2018;378(9):829-839. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29485925>.
6. Brown RM, Wang L, Coston TD, et al. Balanced crystalloids versus saline in sepsis. A secondary analysis of the SMART clinical trial. *Am J Respir Crit Care Med*. 2019;200(12):1487-1495. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31454263>.
7. Antequera Martin AM, Barea Mendoza JA, Muriel A, et al. Buffered solutions versus 0.9% saline for resuscitation in critically ill adults and children. *Cochrane Database Syst Rev*. 2019;7:CD012247. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31334842>.
8. Lewis SR, Pritchard MW, Evans DJ, et al. Colloids versus crystalloids for fluid resuscitation in critically ill people. *Cochrane Database Syst Rev*. 2018;8:CD000567. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30073665>.
9. Delaney AP, Dan A, McCaffrey J, Finfer S. The role of albumin as a resuscitation fluid for patients with sepsis: a systematic review and meta-analysis. *Crit Care Med*. 2011;39(2):386-391. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21248514>.

Oxygenation and Ventilation

Last Updated: December 17, 2020

The COVID-19 Treatment Guidelines Panel's (the Panel's) recommendations below emphasize recommendations from the Surviving Sepsis Campaign Guidelines for [adult sepsis](#), [pediatric sepsis](#), and [COVID-19](#).

Nonmechanically Ventilated Adults With Hypoxemic Respiratory Failure

Recommendations

- For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy, the Panel recommends high-flow nasal cannula (HFNC) oxygen over noninvasive positive pressure ventilation (NIPPV) **(BIIa)**.
- In the absence of an indication for endotracheal intubation, the Panel recommends a closely monitored trial of NIPPV for adults with COVID-19 and acute hypoxemic respiratory failure and for whom HFNC is not available **(BIIa)**.
- For patients with persistent hypoxemia despite increasing supplemental oxygen requirements in whom endotracheal intubation is not otherwise indicated, the Panel recommends considering a trial of awake prone positioning to improve oxygenation **(CIIa)**.
- The Panel **recommends against** using awake prone positioning as a rescue therapy for refractory hypoxemia to avoid intubation in patients who otherwise meet the indications for intubation and mechanical ventilation **(AIII)**.
- If intubation becomes necessary, the procedure should be performed by an experienced practitioner in a controlled setting due to the enhanced risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exposure to health care practitioners during intubation **(AIII)**.

Rationale

Severe illness in COVID-19 typically occurs approximately 1 week after the onset of symptoms. The most common symptom is dyspnea, which is often accompanied by hypoxemia. Patients with severe disease typically require supplemental oxygen and should be monitored closely for worsening respiratory status because some patients may progress to acute respiratory distress syndrome (ARDS).

Goal of Oxygenation

The optimal oxygen saturation (SpO_2) in adults with COVID-19 is uncertain. However, a target SpO_2 of 92% to 96% seems logical considering that indirect evidence from experience in patients without COVID-19 suggests that an $SpO_2 < 92%$ or $> 96%$ may be harmful.

Regarding the potential harm of maintaining an $SpO_2 < 92%$, a trial randomly assigned ARDS patients without COVID-19 to either a conservative oxygen strategy (target SpO_2 of 88% to 92%) or a liberal oxygen strategy (target $SpO_2 \geq 96%$). The trial was stopped early due to futility after enrolling 205 patients, but in the conservative oxygen group there was increased mortality at 90 days (between-group risk difference of 14%; 95% CI, 0.7% to 27%) and a trend toward increased mortality at 28-days (between-group risk difference of 8%; 95% CI, -5% to 21%).¹

Regarding the potential harm of maintaining an $SpO_2 > 96%$, a meta-analysis of 25 randomized trials involving patients without COVID-19 found that a liberal oxygen strategy (median SpO_2 of 96%) was associated with an increased risk of in-hospital mortality compared to a lower SpO_2 comparator (relative

risk 1.21; 95% CI, 1.03–1.43).²

Acute Hypoxemic Respiratory Failure

In adults with COVID-19 and acute hypoxemic respiratory failure, conventional oxygen therapy may be insufficient to meet the oxygen needs of the patient. Options for providing enhanced respiratory support include HFNC, NIPPV, intubation and invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

High-Flow Nasal Cannula and Noninvasive Positive Pressure Ventilation

HFNC is preferred over NIPPV in patients with acute hypoxemic respiratory failure based on data from an unblinded clinical trial in patients without COVID-19 who had acute hypoxemic respiratory failure. Study participants were randomized to HFNC, conventional oxygen therapy, or NIPPV. The patients in the HFNC group had more ventilator-free days (24 days) than those in the conventional oxygen therapy group (22 days) or NIPPV group (19 days) ($P = 0.02$), and 90-day mortality was lower in the HFNC group than in either the conventional oxygen therapy group (HR 2.01; 95% CI, 1.01–3.99) or the NIPPV group (HR 2.50; 95% CI, 1.31–4.78).³ In the subgroup of more severely hypoxemic patients ($\text{PaO}_2/\text{FiO}_2$ mm Hg ≤ 200), the intubation rate was lower for HFNC than for conventional oxygen therapy or NIPPV (HR 2.07 and 2.57, respectively).

The trial's findings were corroborated by a meta-analysis of eight trials with 1,084 patients conducted to assess the effectiveness of oxygenation strategies prior to intubation. Compared to NIPPV, HFNC reduced the rate of intubation (OR 0.48; 95% CI, 0.31–0.73) and ICU mortality (OR 0.36; 95% CI, 0.20–0.63).⁴

NIPPV may generate aerosol spread of SARS-CoV-2 and thus increase nosocomial transmission of the infection.^{5,6} It remains unclear whether HFNC results in a lower risk of nosocomial SARS-CoV-2 transmission than NIPPV.

Prone Positioning for Nonintubated Patients

Although prone positioning has been shown to improve oxygenation and outcomes in patients with moderate-to-severe ARDS who are receiving mechanical ventilation,^{7,8} there is less evidence regarding the benefit of prone positioning in awake patients who require supplemental oxygen without mechanical ventilation. In a case series of 50 patients with COVID-19 pneumonia who required supplemental oxygen upon presentation to a New York City emergency department, awake prone positioning improved the overall median oxygen saturation of the patients. However, 13 patients still required intubation due to respiratory failure within 24 hours of presentation to the emergency department.⁹ Other case series of patients with COVID-19 requiring oxygen or NIPPV have similarly reported that awake prone positioning is well-tolerated and improves oxygenation,¹⁰⁻¹² with some series also reporting low intubation rates after proning.^{10,12}

A prospective feasibility study of awake prone positioning in 56 patients with COVID-19 receiving HFNC or NIPPV in a single Italian hospital found that prone positioning for ≤ 3 hours was feasible in 84% of the patients. There was a significant improvement in oxygenation during prone positioning ($\text{PaO}_2/\text{FiO}_2$ 181 mm Hg in supine position vs. $\text{PaO}_2/\text{FiO}_2$ 286 mm Hg in prone position). However, when compared with baseline oxygenation before initiation of prone positioning, this improvement in oxygenation was not sustained ($\text{PaO}_2/\text{FiO}_2$ of 181 mm Hg and 192 mm Hg at baseline and 1 hour after resupination, respectively). Among patients put in the prone position, there was no difference in intubation rate between patients who maintained improved oxygenation (i.e., responders) and nonresponders.⁹

A prospective, multicenter observational cohort study in Spain and Andorra evaluated the effect of

prone positioning on the rate of intubation in COVID-19 patients with acute respiratory failure receiving HFNC. Of the 199 patients requiring HFNC, 55 (27.6%) were treated with prone positioning. Although the time to intubation was 1 day (IQR 1.0–2.5) in patients receiving HFNC and prone positioning versus 2 days [IQR 1.0–3.0] in patients receiving only HFNC ($P = 0.055$), the use of awake prone positioning did not reduce the risk of intubation (RR 0.87; 95% CI, 0.53–1.43; $P = 0.60$).¹³

Overall, despite promising data, it is unclear which hypoxemic, nonintubated patients with COVID-19 pneumonia benefit from prone positioning, how long prone positioning should be continued, or whether the technique prevents the need for intubation or improves survival.¹⁰

Appropriate candidates for awake prone positioning are those who can adjust their position independently and tolerate lying prone. Awake prone positioning is **contraindicated** in patients who are in respiratory distress and who require immediate intubation. Awake prone positioning is also **contraindicated** in patients who are hemodynamically unstable, patients who recently had abdominal surgery, and patients who have an unstable spine.¹⁴ Awake prone positioning is acceptable and feasible for pregnant patients and can be performed in the left lateral decubitus position or the fully prone position.¹⁵

Intubation for Invasive Mechanical Ventilation

It is essential to monitor hypoxemic patients with COVID-19 closely for signs of respiratory decompensation. To ensure the safety of both patients and health care workers, intubation should be performed in a controlled setting by an experienced practitioner.

Mechanically Ventilated Adults

Recommendations

For mechanically ventilated adults with COVID-19 and ARDS:

- The Panel recommends using low tidal volume (VT) ventilation (VT 4–8 mL/kg of predicted body weight) over higher VT ventilation (VT >8 mL/kg) (**AIIa**).
- The Panel recommends targeting plateau pressures of <30 cm H₂O (**AIIa**).
- The Panel recommends using a conservative fluid strategy over a liberal fluid strategy (**BIIa**).
- The Panel **recommends against** the routine use of inhaled nitric oxide (**AIIa**).

Rationale

There is no evidence that ventilator management of patients with hypoxemic respiratory failure due to COVID-19 should differ from ventilator management of patients with hypoxemic respiratory failure due to other causes.

Positive End-Expiratory Pressure and Prone Positioning in Mechanically Ventilated Adults With Moderate to Severe Acute Respiratory Distress Syndrome

Recommendations

For mechanically ventilated adults with COVID-19 and moderate-to-severe ARDS:

- The Panel recommends using a higher positive end-expiratory pressure (PEEP) strategy over a lower PEEP strategy (**BIIa**).
- For mechanically ventilated adults with COVID-19 and refractory hypoxemia despite optimized ventilation, the Panel recommends prone ventilation for 12 to 16 hours per day over no prone ventilation (**BIIa**).

Rationale

PEEP is beneficial in patients with ARDS because it prevents alveolar collapse, improves oxygenation, and minimizes atelectotrauma, a source of ventilator-induced lung injury. A meta-analysis of individual patient data from the three largest trials that compared lower and higher levels of PEEP in patients without COVID-19 found lower rates of ICU mortality and in-hospital mortality with higher PEEP in those with moderate ($\text{PaO}_2/\text{FiO}_2$ 100–200 mm Hg) and severe ARDS ($\text{PaO}_2/\text{FiO}_2 < 100$ mm Hg).¹⁶

Although there is no clear standard as to what constitutes a high level of PEEP, one conventional threshold is >10 cm H_2O .¹⁷ Recent reports have suggested that, in contrast to patients with non-COVID-19 causes of ARDS, some patients with moderate or severe ARDS due to COVID-19 have normal static lung compliance and thus, in these patients, higher PEEP levels may cause harm by compromising hemodynamics and cardiovascular performance.^{18,19} Other studies reported that patients with moderate to severe ARDS due to COVID-19 had low compliance, similar to the lung compliance seen in patients with conventional ARDS.²⁰⁻²³ These seemingly contradictory observations suggest that COVID-19 patients with ARDS are a heterogeneous population and assessment for responsiveness to higher PEEP should be individualized based on oxygenation and lung compliance. Clinicians should monitor patients for known side effects of higher PEEP, such as barotrauma and hypotension.

Neuromuscular Blockade in Mechanically Ventilated Adults With Moderate to Severe Acute Respiratory Distress Syndrome

Recommendations

For mechanically ventilated adults with COVID-19 and moderate-to-severe ARDS:

- The Panel recommends using, as needed, intermittent boluses of neuromuscular blocking agents (NMBA) or continuous NMBA infusion to facilitate protective lung ventilation (**BIIa**).
- In the event of persistent patient-ventilator dyssynchrony, or in cases where a patient requires ongoing deep sedation, prone ventilation, or persistently high plateau pressures, the Panel recommends using a continuous NMBA infusion for up to 48 hours as long as patient anxiety and pain can be adequately monitored and controlled (**BIII**).

Rationale

The recommendation for intermittent boluses of NMBA or continuous infusion of NMBA to facilitate lung protection may require a health care provider to enter the patient's room frequently for close clinical monitoring. Therefore, in some situations, the risks of SARS-CoV-2 exposure and the need to use personal protective equipment for each entry into a patient's room may outweigh the benefit of NMBA treatment.

Rescue Therapies for Mechanically Ventilated Adults With Acute Respiratory Distress Syndrome

Recommendations

For mechanically ventilated adults with COVID-19, severe ARDS, and hypoxemia despite optimized ventilation and other rescue strategies:

- The Panel recommends using recruitment maneuvers rather than not using recruitment maneuvers (**CIIa**).
- If recruitment maneuvers are used, the Panel **recommends against** using staircase (incremental PEEP) recruitment maneuvers (**AIIIa**).

- The Panel recommends using an inhaled pulmonary vasodilator as a rescue therapy; if no rapid improvement in oxygenation is observed, the treatment should be tapered off (CIII).

Rationale

There are no studies to date assessing the effect of recruitment maneuvers on oxygenation in severe ARDS due to COVID-19. However, a systematic review and meta-analysis of six trials of recruitment maneuvers in non-COVID-19 patients with ARDS found that recruitment maneuvers reduced mortality, improved oxygenation 24 hours after the maneuver, and decreased the need for rescue therapy.²⁴ Because recruitment maneuvers can cause barotrauma or hypotension, patients should be closely monitored during recruitment maneuvers. If a patient decompensates during recruitment maneuvers, the maneuver should be stopped immediately. The importance of properly performing recruitment maneuvers was illustrated by an analysis of eight randomized controlled trials in non-COVID-19 patients (n = 2,544) which found that recruitment maneuvers did not reduce hospital mortality (RR 0.90; 95% CI, 0.78–1.04). Subgroup analysis found that traditional recruitment maneuvers significantly reduced hospital mortality (RR 0.85; 95% CI, 0.75–0.97), whereas incremental PEEP titration recruitment maneuvers increased mortality (RR 1.06; 95% CI, 0.97–1.17).²⁵

Although there are no published studies of inhaled nitric oxide in patients with COVID-19, a Cochrane review of 13 trials of inhaled nitric oxide use in patients with ARDS found no mortality benefit.²⁶ Because the review showed a transient benefit in oxygenation, it is reasonable to attempt inhaled nitric oxide as a rescue therapy in COVID patients with severe ARDS after other options have failed. However, if there is no benefit in oxygenation with inhaled nitric oxide, it should be tapered quickly to avoid rebound pulmonary vasoconstriction that may occur with discontinuation after prolonged use.

References

1. Barrot L, Asfar P, Mauny F, et al. Liberal or conservative oxygen therapy for acute respiratory distress syndrome. *N Engl J Med*. 2020;382(11):999-1008. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32160661>.
2. Chu DK, Kim LH, Young PJ, et al. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. *Lancet*. 2018;391(10131):1693-1705. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29726345>.
3. Frat JP, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med*. 2015;372(23):2185-2196. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25981908>.
4. Ni YN, Luo J, Yu H, Liu D, Liang BM, Liang ZA. The effect of high-flow nasal cannula in reducing the mortality and the rate of endotracheal intubation when used before mechanical ventilation compared with conventional oxygen therapy and noninvasive positive pressure ventilation. A systematic review and meta-analysis. *Am J Emerg Med*. 2018;36(2):226-233. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28780231>.
5. Tran K, Cimon K, Severn M, Pessoa-Silva CL, Conly J. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review. *PLoS One*. 2012;7(4):e35797. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22563403>.
6. Yu IT, Xie ZH, Tsoi KK, et al. Why did outbreaks of severe acute respiratory syndrome occur in some hospital wards but not in others? *Clin Infect Dis*. 2007;44(8):1017-1025. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17366443>.
7. Guerin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med*. 2013;368(23):2159-2168. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23688302>.
8. Fan E, Del Sorbo L, Goligher EC, et al. An official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice guideline: mechanical ventilation in adult

- patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2017;195(9):1253-1263. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28459336>.
9. Caputo ND, Strayer RJ, Levitan R. Early self-proning in awake, non-intubated patients in the emergency department: a single ED's experience during the COVID-19 pandemic. *Acad Emerg Med*. 2020;27(5):375-378. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32320506>.
 10. Sun Q, Qiu H, Huang M, Yang Y. Lower mortality of COVID-19 by early recognition and intervention: experience from Jiangsu Province. *Ann Intensive Care*. 2020;10(1):33. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32189136>.
 11. Elharrar X, Trigui Y, Dols AM, et al. Use of prone positioning in nonintubated patients With COVID-19 and hypoxemic acute respiratory failure. *JAMA*;2020;323(22):2336-2338. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32412581>.
 12. Sartini C, Tresoldi M, Scarpellini P, et al. Respiratory parameters in patients with COVID-19 after using noninvasive ventilation in the prone position outside the intensive care unit. *JAMA*. 2020;323(22):2338-2340. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32412606>.
 13. Ferrando C, Mellado-Artigas R, Gea A, et al. Awake prone positioning does not reduce the risk of intubation in COVID-19 treated with high-flow nasal oxygen therapy: a multicenter, adjusted cohort study. *Crit Care*. 2020;24(1):597. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33023669>.
 14. Bamford P, Bentley A, Dean J, Whitmore D, Wilson-Baig N. ICS guidance for prone positioning of the conscious COVID patient. *Intensive Care Society*. 2020. Available at: <https://emcrit.org/wp-content/uploads/2020/04/2020-04-12-Guidance-for-conscious-proning.pdf>. Accessed December 8, 2020.
 15. Society for Maternal Fetal Medicine. Management considerations for pregnant patients with COVID-19. 2020. Available at: https://s3.amazonaws.com/cdn.smfm.org/media/2336/SMFM_COVID_Management_of_COVID_pos_preg_patients_4-30-20_final.pdf. Accessed December 8, 2020.
 16. Briel M, Meade M, Mercat A, et al. Higher vs. lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *JAMA*. 2010;303(9):865-873. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20197533>.
 17. Alhazzani W, Moller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). *Crit Care Med*. 2020;48(6):e440-e469. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32224769>.
 18. Marini JJ, Gattinoni L. Management of COVID-19 respiratory distress. *JAMA*. 2020;323(22):2329-2330. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32329799>.
 19. Tsolaki V, Siempos I, Magira E, Kokkoris S, Zakyntinos GE, Zakyntinos S. PEEP levels in COVID-19 pneumonia. *Crit Care*. 2020;24(1):303. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32505186>.
 20. Bhatraju PK, Ghassemieh BJ, Nichols M, et al. COVID-19 in critically ill patients in the Seattle region - case series. *N Engl J Med*. 2020;382(21):2012-2022. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32227758>.
 21. Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. *Lancet*. 2020;395(10239):1763-1770. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32442528>.
 22. Ziehr DR, Alladina J, Petri CR, et al. Respiratory pathophysiology of mechanically ventilated patients with COVID-19: a cohort study. *Am J Respir Crit Care Med*. 2020;201(12):1560-1564. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32348678>.
 23. Schenck EJ, Hoffman K, Goyal P, et al. Respiratory mechanics and gas exchange in COVID-19 associated respiratory failure. *Ann Am Thorac Soc*. 2020;17(9):1158-1161. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32432896>.
 24. Goligher EC, Hodgson CL, Adhikari NKJ, et al. Lung recruitment maneuvers for adult patients with acute respiratory distress syndrome. a systematic review and meta-analysis. *Ann Am Thorac Soc*. 2017;14(Supplement 4):S304-S311. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29043837>.

25. Alhazzani W, Moller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Intensive Care Med.* 2020;46(5):854-887. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32222812>.
26. Gebistorf F, Karam O, Wetterslev J, Afshari A. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) in children and adults. *Cochrane Database Syst Rev.* 2016(6):CD002787. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27347773>.

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.

References

1. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5,700 patients hospitalized with COVID-19 in the New York City area. *JAMA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32320003>.
2. American Society of Nephrology. Recommendations on the care of hospitalized patients with COVID-19 and kidney failure requiring renal replacement therapy. 2020. Available at: https://www.asn-online.org/g/blast/files/AKI_COVID-19_Recommendations_Document_03.21.2020.pdf. Accessed November 20, 2020.
3. Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19): considerations for providing hemodialysis to patients with suspected or confirmed COVID-19 in acute care settings. 2020. Available at: <https://www.cdc.gov/coronavirus/2019-ncov/hcp/dialysis/dialysis-in-acute-care.html>. Accessed November 19, 2020.

Pharmacologic Interventions

Last Updated: October 9, 2020

Antiviral Therapy

See [Therapeutic Management of Patients with COVID-19](#) for recommendations on the use of remdesivir with or without corticosteroids.

Immune-Based Therapy

Several immune-based therapies that are expected to modify the course of COVID-19, including corticosteroids, are currently under investigation or are already in use. These agents may target the virus (e.g., convalescent plasma) or modulate the immune response (e.g., corticosteroids, interleukin [IL]-1 or IL-6 inhibitors). Recommendations regarding immune-based therapy can be found in [Immunomodulators Under Evaluation for the Treatment of COVID-19](#).

Corticosteroids

See [Therapeutic Management of Patients with COVID-19](#) for recommendations on the use of dexamethasone with or without remdesivir.

Adjunctive Therapy

Recommendations for using adjunctive therapy in a critical care setting can be found in the [Antithrombotic Therapy](#) and [Vitamin C](#) sections.

Empiric Broad-Spectrum Antimicrobial Therapy

Recommendations

- In patients with COVID-19 and severe or critical illness, there are insufficient data to recommend empiric broad-spectrum antimicrobial therapy in the absence of another indication.
- If antimicrobials are initiated, the Panel recommends that their use should be reassessed daily in order to minimize the adverse consequences of unnecessary antimicrobial therapy (**AIII**).

Rationale

There are no reliable estimates of the incidence or prevalence of copathogens with severe acute respiratory syndrome coronavirus 2 at this time.

Some experts routinely administer broad-spectrum antibiotics as empiric therapy for bacterial pneumonia to all patients with COVID-19 and moderate or severe hypoxemia. Other experts administer antibiotics only for specific situations, such as the presence of a lobar infiltrate on a chest X-ray, leukocytosis, an elevated serum lactate level, microbiologic data, or shock.

Gram stain, culture, or other testing of respiratory specimens is often not available due to concerns about aerosolization of the virus during diagnostic procedures or when processing specimens.

There are no clinical trials that have evaluated the use of empiric antimicrobial agents in patients with COVID-19 or other severe coronavirus infections.

Extracorporeal Membrane Oxygenation

Last Updated: December 17, 2020

Recommendation

- There are insufficient data to recommend either for or against the use of extracorporeal membrane oxygenation (ECMO) in patients with COVID-19 and refractory hypoxemia.

Rationale

ECMO has been used as a short-term rescue therapy in patients with acute respiratory distress syndrome (ARDS) caused by COVID-19 and refractory hypoxemia. However, there is no conclusive evidence that ECMO is responsible for better clinical outcomes regardless of the cause of hypoxemic respiratory failure.¹⁻⁴

The clinical outcomes for patients with ARDS who are treated with ECMO are variable and depend on multiple factors, including the etiology of hypoxemic respiratory failure, the severity of pulmonary and extrapulmonary illness, the presence of comorbidities, and the ECMO experience of the individual center.⁵⁻⁷ A recent case series of 83 COVID-19 patients in Paris reported a 60-day mortality of 31% for patients on ECMO.⁸ This mortality was similar to the mortality observed in a 2018 study of non-COVID-19 patients with ARDS who were treated with ECMO during the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial; that study reported a mortality of 35% at Day 60.³

The Extracorporeal Life Support Organization (ELSO) Registry provides the largest multicenter outcome dataset of patients with confirmed COVID-19 who received ECMO support and whose data were voluntarily submitted. A recent cohort study evaluated ELSO Registry data for 1,035 COVID-19 patients who initiated ECMO between January 16 and May 1, 2020, at 213 hospitals in 36 countries. This study reported an estimated cumulative in-hospital mortality of 37.4% in these patients 90 days after they initiated ECMO (95% CI; 34.4% to 40.4%).⁹ Without a controlled trial that evaluates the use of ECMO in patients with COVID-19 and hypoxemic respiratory failure (e.g., ARDS), the benefits of ECMO cannot be clearly defined for this patient population.

Ideally, clinicians who are interested in using ECMO should try to enter their patients into clinical trials or clinical registries so that more informative data can be obtained. The following resources provide more information on the use of ECMO in patients with COVID-19:

- [The ELSO ECMO in COVID-19 website](#)
- A list of [clinical trials that are evaluating ECMO in patients with COVID-19](#) on [ClinicalTrials.gov](#)

References

1. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet*. 2009;374(9698):1351-1363. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19762075>.
2. Pham T, Combes A, Roze H, et al. Extracorporeal membrane oxygenation for pandemic influenza A(H1N1)-induced acute respiratory distress syndrome: a cohort study and propensity-matched analysis. *Am J Respir Crit Care Med*. 2013;187(3):276-285. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23155145>.
3. Combes A, Hajage D, Capellier G, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med*. 2018;378(21):1965-1975. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29791822>.

4. Munshi L, Walkey A, Goligher E, Pham T, Uleryk EM, Fan E. Venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: a systematic review and meta-analysis. *Lancet Respir Med*. 2019;7(2):163-172. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30642776>.
5. Bullen EC, Teijeiro-Paradis R, Fan E. How I select which patients with ARDS should be treated with venovenous extracorporeal membrane oxygenation. *Chest*. 2020;158(3):1036-1045. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32330459>.
6. Henry BM, Lippi G. Poor survival with extracorporeal membrane oxygenation in acute respiratory distress syndrome (ARDS) due to coronavirus disease 2019 (COVID-19): Pooled analysis of early reports. *J Crit Care*. 2020;58:27-28. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32279018>.
7. Mustafa AK, Alexander PJ, Joshi DJ, et al. Extracorporeal membrane oxygenation for patients with COVID-19 in severe respiratory failure. *JAMA Surg*. 2020;Published online ahead of print. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32780089>.
8. Schmidt M, Hajage D, Lebreton G, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome associated with COVID-19: a retrospective cohort study. *Lancet Respir Med*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32798468>.
9. Barbaro RP, MacLaren G, Boonstra PS, et al. Extracorporeal membrane oxygenation support in COVID-19: an international cohort study of the Extracorporeal Life Support Organization registry. *Lancet*. 2020;396(10257):1071-1078. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32987008>.

Therapeutic Management of Patients With COVID-19

Last Updated: February 11, 2021

Executive Summary

Two main processes are thought to drive the pathogenesis of COVID-19. Early in the course of the infection, the disease is primarily driven by replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Later in the course of infection, the disease is driven by an exaggerated immune/inflammatory response to the virus that leads to tissue damage. Based on this understanding, it is anticipated that antiviral therapies would have the greatest effect early in the course of disease, while immunosuppressive/anti-inflammatory therapies are likely to be more beneficial in the later stages of COVID-19.

In the earliest stages of infection, before the host has mounted an effective immune response, anti-SARS-CoV-2 antibody-based therapies may have their greatest likelihood of having an effect. In this regard, although there are insufficient data from clinical trials to recommend either for or against the use of any specific therapy in this setting, preliminary data suggests that outpatients may benefit from receiving anti-SARS-CoV-2 monoclonal antibodies early in the course of infection. The Food and Drug Administration (FDA) has issued Emergency Use Authorizations (EUAs) for certain anti-SARS-CoV-2 monoclonal antibodies for the treatment of outpatients with mild to moderate COVID-19; please see [Anti-SARS-CoV-2 Monoclonal Antibodies](#) for more information.

Remdesivir, an antiviral agent, is currently the only drug that is approved by the FDA for the treatment of COVID-19. It is recommended for use in hospitalized patients who require supplemental oxygen. However, it is not routinely recommended for patients who require mechanical ventilation due to the lack of data showing benefit at this advanced stage of the disease.¹⁻⁴

Dexamethasone, a corticosteroid, has been found to improve survival in hospitalized patients who require supplemental oxygen, with the greatest effect observed in patients who require mechanical ventilation. Therefore, the use of dexamethasone is strongly recommended in this setting.⁵⁻⁸

The COVID-19 Treatment Guidelines Panel (the Panel) continues to review the most recent clinical data to provide up-to-date treatment recommendations for clinicians who are caring for patients with COVID-19. Figure 1 summarizes the Panel's recommendations for managing patients with varying severities of disease.

Figure 1. Pharmacologic Management of Patients with COVID-19 Based on Disease Severity

Doses and durations are listed in the footnote.

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS
<p>Not Hospitalized, Mild to Moderate COVID-19</p>	<p>There are insufficient data to recommend either for or against any specific antiviral or antibody therapy. SARS-CoV-2 neutralizing antibodies (bamlanivimab or casirivimab plus imdevimab) are available through EUAs for outpatients who are at high risk of disease progression.^a</p> <p>The Panel recommends against the use of dexamethasone or other corticosteroids (AIII).^b</p>
<p>Hospitalized but Does Not Require Supplemental Oxygen</p>	<p>The Panel recommends against the use of dexamethasone (AIIa) or other corticosteroids (AIII).^b</p> <p>There are insufficient data to recommend either for or against the routine use of remdesivir. For patients at high risk of disease progression, the use of remdesivir may be appropriate.</p>
<p>Hospitalized and Requires Supplemental Oxygen (But Does Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO)</p>	<p>Use one of the following options:</p> <ul style="list-style-type: none"> • Remdesivir^{c,d} (e.g., for patients who require minimal supplemental oxygen) (BIIa) • Dexamethasone^e plus remdesivir^{c,d} (e.g., for patients who require increasing amounts of supplemental oxygen) (BIII)^{f,g} • Dexamethasone^e (e.g., when combination therapy with remdesivir cannot be used or is not available) (BI)
<p>Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation</p>	<p>Use one of the following options:</p> <ul style="list-style-type: none"> • Dexamethasone^{e,g} (AI) • Dexamethasone^e plus remdesivir^{c,d} (BIII)^{f,g}
<p>Hospitalized and Requires Invasive Mechanical Ventilation or ECMO</p>	<p>Dexamethasone^e (AI)^h</p>
<p>Rating of Recommendations: A = Strong; B = Moderate; C = Optional Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion</p>	

^a See the Anti-SARS-CoV-2 Monoclonal Antibodies section for more information on using bamlanivimab and casirivimab plus imdevimab in patients with mild to moderate COVID-19.

^b Patients who are receiving corticosteroids for other indications should continue therapy for their underlying conditions as directed by their health care providers.

^c The remdesivir dose is 200 mg IV for one dose, followed by remdesivir 100 mg IV once daily for 4 days or until hospital discharge (unless the patient is in a health care setting that can provide acute care that is similar to inpatient hospital care). Treatment duration may be extended to up to 10 days if there is no substantial clinical improvement by Day 5.

^d For patients who are receiving remdesivir but progress to requiring oxygen through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or ECMO, remdesivir should be continued until the treatment course is completed.

^e The dexamethasone dose is 6 mg IV or PO once daily for 10 days or until hospital discharge. If dexamethasone is not available, equivalent doses of other corticosteroids (e.g., prednisone, methylprednisolone, hydrocortisone) may be used. See the Corticosteroids section for more information.

^f The combination of dexamethasone and remdesivir has not been studied in clinical trials.

^g In the rare circumstances where corticosteroids cannot be used, **baricitinib plus remdesivir** can be used **(BIIa)**. The FDA has issued an EUA for baricitinib use in combination with remdesivir. The dose for baricitinib is 4 mg PO once daily for 14 days or until hospital discharge.

^h The combination of **dexamethasone and remdesivir** may be considered for patients who have recently been intubated **(CIII)**. The Panel **recommends against** the use of remdesivir monotherapy in these patients.

Key: ECMO = extracorporeal membrane oxygenation; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; IV = intravenous; the Panel = the COVID-19 Treatment Guidelines Panel; PO = orally; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

Patients With Mild to Moderate COVID-19 Who Are Not Hospitalized

For definitions of the clinical severity categories for patients with COVID-19, please see [Clinical Spectrum of SARS-CoV-2 Infection](#).

Recommendations

- There are insufficient data for the Panel to recommend either for or against the use of any specific antiviral or antibody therapy in these patients.
- SARS-CoV-2-neutralizing antibodies (bamlanivimab or casirivimab plus imdevimab) are available through EUAs for outpatients who have a high risk of disease progression. These EUAs do not authorize use in hospitalized patients.
- The Panel **recommends against** the use of **dexamethasone** or **other corticosteroids (AIII)**. Patients who are receiving dexamethasone or another corticosteroid for other indications should continue therapy for their underlying conditions as directed by their health care provider.

Rationale for the Panel’s Assessment That There Are Insufficient Data to Recommend Either For or Against the Use of Specific Antibody Therapy

Preliminary data from two small randomized controlled trials (BLAZE-1 and R10933-10987-COV-2067) suggested that anti-SARS-CoV-2 monoclonal antibody products may reduce the number of visits to emergency departments or hospitalizations in outpatients with mild to moderate COVID-19 (see [Anti-SARS-CoV-2 Monoclonal Antibodies: Selected Clinical Data](#)).^{9,10} As a result of these studies, the FDA issued EUAs for two products—a single monoclonal antibody, bamlanivimab, and a combination of two antibodies, casirivimab plus imdevimab—for use in outpatients with a high risk of disease progression.^{10,11} However, these studies enrolled a relatively small number of participants, and most of these participants were aged <65 years. In addition, the low number of clinical events that occurred during these trials (hospitalizations or emergency department visits) make it difficult to draw definitive conclusions regarding the efficacy of these antibodies.

Because of these limitations, there are insufficient data for the Panel to recommend either for or against the use of these anti-SARS-CoV-2 monoclonal antibodies (bamlanivimab or casirivimab plus imdevimab) in nonhospitalized patients with mild to moderate COVID-19. Ongoing clinical trials will provide further evidence on the safety and efficacy of these agents. Health care providers are encouraged to discuss participation in anti-SARS-CoV-2 monoclonal antibody clinical trials with their patients, if any trials are available. Clinicians are encouraged to discuss the potential benefits and risks of using these products with high-risk patients who meet the EUA criteria for these antibodies.

Rationale for the Panel’s Assessment That There Are Insufficient Data to Recommend Either For or Against the Use of Specific Antiviral Therapies

Completed clinical trials evaluating the use of remdesivir for treating mild to moderate COVID-19 have been limited to hospitalized patients. An ongoing clinical trial is evaluating the use of remdesivir in outpatients with COVID-19; the results from this study will further inform the role of remdesivir in this setting.

Rationale for Recommending Against the Use of Dexamethasone or Other Corticosteroids

Dexamethasone was studied in hospitalized patients with COVID-19 and was found to reduce mortality in patients who required supplemental oxygen.⁵ Outpatients with mild to moderate COVID-19 were not included in this trial; therefore, the safety and efficacy of using corticosteroids in this population have not been studied. The Panel **recommends against** the use of **corticosteroids** in this population because

there are no clinical trial data to support their use (**AIII**). Moreover, the use of corticosteroids can lead to adverse events, such as hyperglycemia, neuropsychiatric symptoms, and superinfections. These events are more difficult to monitor in an outpatient setting. Outpatients who are receiving dexamethasone or another corticosteroid for other indications should continue therapy for their underlying conditions as directed by their health care provider. Please see [Corticosteroids: Selected Clinical Data](#) for additional information.

Patients Who Are Hospitalized With Moderate COVID-19 but Who Do Not Require Supplemental Oxygen

Recommendations

- The Panel **recommends against** the use of **dexamethasone** or **other corticosteroids (AIIa)**. Patients who are receiving dexamethasone or another corticosteroid for other indications should continue therapy for their underlying conditions as directed by their health care provider.
- There are insufficient data to recommend either for or against the routine use of remdesivir in these patients. The use of remdesivir may be appropriate in patients who have a high risk of disease progression.

Rationale for Recommending Against the Use of Dexamethasone or Other Corticosteroids

In the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial, a multicenter, open-label trial in the United Kingdom, hospitalized patients with COVID-19 were randomized to receive either dexamethasone plus standard of care or standard of care alone (control arm).⁵ In the subgroup of participants who did not require supplemental oxygen at enrollment, no survival benefit was observed for dexamethasone: 17.8% of participants in the dexamethasone arm and 14% in the control arm died within 28 days of enrollment (rate ratio 1.19; 95% CI, 0.91–1.55). Please see [Corticosteroids: Selected Clinical Data](#) for additional information. Based on these data, the Panel **recommends against** the use of **dexamethasone (AIIa)** or **other corticosteroids (AIII)** for the treatment of COVID-19 in this subgroup, unless the patient has another indication for corticosteroid therapy.

Rationale for the Panel’s Assessment That There Are Insufficient Data to Recommend Either For or Against the Use of Remdesivir

The Adaptive COVID-19 Treatment Trial (ACTT-1) was a multinational randomized controlled trial that compared remdesivir to placebo in hospitalized patients with COVID-19. Remdesivir showed no significant benefit in patients with mild to moderate disease, which was defined as oxygen saturation >94% on room air or a respiratory rate <24 breaths/min without supplemental oxygen (rate ratio for recovery 1.29; 95% CI, 0.91–1.83); however, there were only 138 patients in this group.¹

In a manufacturer-sponsored, open-label randomized trial of 596 patients with moderate COVID-19, patients who received 5 days of remdesivir had higher odds of having a better clinical status on Day 11 (based on distribution on a seven-point ordinal scale) than those who received standard of care (OR 1.65; 95% CI, 1.09–2.48; $P = 0.02$). However, the difference between the groups was of uncertain clinical importance.³

In the Solidarity trial, about 25% of hospitalized patients in the remdesivir and control arms did not require supplemental oxygen at study entry. The primary outcome of in-hospital mortality occurred in 2% of patients (11 of 661) in the remdesivir arm and 2.1% of patients (13 of 664) in the control arm (rate ratio 0.90; 99% CI, 0.31–2.58).¹² The open-label design of this study makes it difficult to determine whether remdesivir affects recovery time as determined by duration of hospitalization, because patient discharge may have been delayed in order to complete remdesivir therapy. Please see [Remdesivir:](#)

[Selected Clinical Data](#) for additional information.

Because these three trials produced conflicting results regarding the benefits of remdesivir, the Panel finds the available data insufficient to recommend either for or against routine treatment with remdesivir for all hospitalized patients with moderate COVID-19. However, the Panel recognizes that there may be situations in which a clinician judges that remdesivir is an appropriate treatment for a hospitalized patient with moderate disease (e.g., a person who is at a particularly high risk for clinical deterioration).

For Hospitalized Patients With COVID-19 Who Require Supplemental Oxygen but Who Do Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or Extracorporeal Membrane Oxygenation

Recommendations

The Panel recommends one of the following options for these patients:

- **Remdesivir** (e.g., for patients who require minimal supplemental oxygen) (**BIIa**);
- **Dexamethasone plus remdesivir** (e.g., for patients who require increasing amounts of oxygen) (**BIII**); *or*
- **Dexamethasone** (e.g., when combination therapy with remdesivir cannot be used or is not available) (**BI**).

Additional Considerations

- If dexamethasone is not available, an alternative corticosteroid such as **prednisone**, **methylprednisolone**, or **hydrocortisone** can be used (**BIII**). See [Corticosteroids](#) for dosing recommendations.
- In the rare circumstances when corticosteroids cannot be used, **baricitinib plus remdesivir** can be used (**BIIa**). Baricitinib **should not be used** without remdesivir.

Rationale for the Use of Remdesivir

In ACTT-1, remdesivir was associated with improved time to recovery in the subgroup of participants (n = 435) who required oxygen supplementation but not high-flow oxygen, noninvasive ventilation, or mechanical ventilation (7 days for remdesivir vs. 9 days for placebo; recovery rate ratio 1.45; 95% CI, 1.18–1.79). A lower percentage of patients in the remdesivir arm than in the placebo arm progressed to requiring high-flow oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) among those who were not using these methods of oxygen delivery at baseline (17% vs. 24%). In a post hoc analysis of deaths by Day 29, remdesivir appeared to confer a substantial survival benefit in this subgroup (HR for death 0.30; 95% CI, 0.14–0.64).¹

The Solidarity trial was a large, multinational, open-label randomized controlled trial in which a 10-day course of remdesivir was compared to standard of care. This trial reported no difference in the rate of in-hospital deaths between patients who received remdesivir and those who received standard of care (rate ratio of death 0.95; 95% CI, 0.81–1.11 in the overall study population; rate ratio of death 0.86; 99% CI, 0.67–1.11 for patients who did not require mechanical ventilation at entry). There was no difference between patients who received remdesivir and those who received standard of care in the percentage of patients who progressed to invasive mechanical ventilation (11.9% vs. 11.5%) or in length of hospital stay.¹² However, an open-label trial like Solidarity is less well-suited than a placebo-controlled trial to assess time to recovery. In Solidarity, because both clinicians and patients knew that remdesivir

was being administered, it is possible that the hospital discharge could have been delayed in order to complete the 10-day course of therapy.

During ACTT-1, remdesivir hastened the time to recovery in patients who required minimal supplemental oxygen. Based on these results and data from other studies, the Panel recommends **remdesivir** (without dexamethasone) as a treatment option for patients in this group (**BIIa**). In these individuals, the hyperinflammatory state where corticosteroids might be considered most beneficial may not yet be present or fully developed. For more information, please see [Remdesivir: Selected Clinical Data](#).

Rationale for the Use of Remdesivir Plus Dexamethasone

The safety and efficacy of using remdesivir plus dexamethasone for the treatment of COVID-19 have not been rigorously evaluated in clinical trials. Despite the lack of clinical trial data, there is a theoretical rationale for combining remdesivir and dexamethasone (see the discussion of clinical trial data for remdesivir above and the discussion for dexamethasone below). Patients with severe COVID-19 may develop a systemic inflammatory response that leads to multiple organ dysfunction syndrome. The potent anti-inflammatory effects of corticosteroids might prevent or mitigate these hyperinflammatory effects. Thus, the combination of an antiviral agent, such as remdesivir, with an anti-inflammatory agent, such as dexamethasone, may treat the viral infection and dampen the potentially injurious inflammatory response that is a consequence of the infection.

Based on these theoretical considerations, the Panel recommends the combination of **dexamethasone plus remdesivir** as a treatment option for patients in this group (e.g., in those who require increasing amounts of supplemental oxygen) (**BIII**).

Rationale for the Use of Dexamethasone

In the RECOVERY trial, treatment with dexamethasone conferred a survival benefit among participants who required supplemental oxygen at enrollment. In the dexamethasone group, 23.3% of participants died within 28 days of enrollment compared with 26.2% in the standard of care arm (rate ratio 0.82; 95% CI, 0.72–0.94).⁵ However, the amount of supplemental oxygen that participants were receiving and the proportions of participants who required oxygen delivery through a high-flow device or noninvasive ventilation were not reported. It is possible that the benefit of dexamethasone was greatest in those who required more respiratory support. It should be noted that <0.1% of patients in the RECOVERY trial received concomitant remdesivir. For more information, please see the [Corticosteroids](#) section.

However, some experts prefer not to use dexamethasone monotherapy in this group because of the theoretical concern that corticosteroids might slow viral clearance when they are administered without an antiviral drug. Corticosteroids have been associated with delayed viral clearance and/or worse clinical outcomes in patients with other viral respiratory infections.¹³⁻¹⁵ Some studies, but not all, have suggested that corticosteroids slow SARS-CoV-2 clearance, but the results to date are inconclusive.¹⁶⁻²⁰

Rationale for the Use of Baricitinib Plus Remdesivir When Corticosteroids Cannot Be Administered

In the ACTT-2 study, 1,033 hospitalized patients with COVID-19 were randomized to receive baricitinib (a Janus kinase inhibitor) plus remdesivir or placebo plus remdesivir. Among all participants, the median time to recovery was shorter with baricitinib plus remdesivir (7 days) than with remdesivir alone (8 days; rate ratio 1.16; 95% CI, 1.01–1.32; $P = 0.03$). New use of oxygen or mechanical ventilation was less likely with baricitinib plus remdesivir than with remdesivir alone, as were serious adverse events and new infections.

In a subgroup analysis of participants who required supplemental oxygen but who did not receive it through a high-flow device or invasive mechanical ventilation, the rate ratio for recovery was 1.17 (95% CI, 0.98–1.39). There was no statistically significant difference in mortality by Day 28 between the baricitinib and placebo arms in this subgroup (OR 0.4; 95% CI, 0.14–1.14) or in the overall population. Baseline corticosteroid use was an exclusion criterion, and the trial enrolled most participants prior to the public release of RECOVERY data.

Because dexamethasone has been shown to reduce mortality among patients who required supplemental oxygen, clinicians should prioritize the use of dexamethasone in this subgroup. The Panel therefore reserves **baricitinib plus remdesivir** for the rare circumstances in which corticosteroids are contraindicated (**BIIa**). It is unknown whether baricitinib would have an additive benefit or adverse effects when given in combination with corticosteroids. Therefore, the Panel **recommends against** using the combination of **baricitinib, dexamethasone, and remdesivir**, except in a clinical trial (**BIII**).

For Hospitalized Patients With COVID-19 Who Require Delivery of Oxygen Through a High-Flow Device or Noninvasive Ventilation but Not Invasive Mechanical Ventilation or Extracorporeal Membrane Oxygenation

Recommendations

The Panel recommends one of the following options for these patients:

- **Dexamethasone** alone (**AI**); *or*
- A combination of **dexamethasone plus remdesivir** (**BIII**).

Additional Considerations

- The combination of dexamethasone and remdesivir has not been rigorously studied in clinical trials. Because there are theoretical reasons for combining these drugs, the Panel considers both dexamethasone alone and the combination of remdesivir and dexamethasone to be acceptable options for treating COVID-19 in this group of patients.
- The Panel **recommends against** the use of **remdesivir alone** because it is not clear whether remdesivir confers a clinical benefit in this group of patients (**AIIa**).
- For patients who initially received remdesivir monotherapy and progressed to requiring high-flow oxygen or noninvasive ventilation, dexamethasone should be initiated and remdesivir should be continued until the treatment course is completed.
- If dexamethasone is not available, equivalent doses of other corticosteroids such as **prednisone**, **methylprednisolone**, or **hydrocortisone** may be used (**BIII**). See [Corticosteroids](#) for more information.
- In the rare circumstances where corticosteroids cannot be used, **baricitinib plus remdesivir** can be used (**BIIa**). Baricitinib **should not be used** without remdesivir.

Rationale for the Use of Dexamethasone

In the RECOVERY study, treatment with dexamethasone conferred a survival benefit among participants who required supplemental oxygen without invasive mechanical ventilation at enrollment: 23.3% of the participants in the dexamethasone group died within 28 days of enrollment compared with 26.2% in the standard of care arm (rate ratio 0.82; 95% CI, 0.72–0.94).⁵

Rationale for the Use of Remdesivir Plus Dexamethasone

The combination of remdesivir and dexamethasone has not been rigorously studied in clinical trials; therefore, the safety and efficacy of this combination are unknown. The Panel recognizes that there are theoretical reasons to use the combination of remdesivir and dexamethasone, as described above. Based on these theoretical considerations, the Panel considers the combination of dexamethasone plus remdesivir a treatment option for patients in this group (e.g., in those who require delivery of oxygen through a high-flow device or noninvasive ventilation).

Rationale for Not Recommending Remdesivir Monotherapy

In ACTT-1, there was no observed difference in time to recovery between the remdesivir and placebo groups (recovery rate ratio 1.09; 95% CI, 0.76–1.57) in the subgroup of participants who required high-flow oxygen or noninvasive ventilation at enrollment (n = 193). A post hoc analysis did not show a survival benefit for remdesivir at Day 29.¹ However, the trial was not powered to detect differences in outcomes within subgroups. The Panel **does not recommend** using **remdesivir monotherapy** in these patients because there is uncertainty regarding whether remdesivir alone confers a clinical benefit in this subgroup (**AIIa**). Dexamethasone or remdesivir plus dexamethasone are better treatment options for COVID-19 in this group of patients.

For patients who start remdesivir monotherapy and then progress to requiring oxygen delivery through a high-flow device or noninvasive ventilation, the Panel recommends initiating dexamethasone and continuing remdesivir until the treatment course is completed. Clinical trials that evaluated the use of remdesivir categorized patients based on their severity of illness at the start of treatment with remdesivir; therefore, patients may benefit from remdesivir even if their clinical course progresses to a severity of illness for which the benefits of remdesivir are less certain.

Rationale for the Use of Baricitinib Plus Remdesivir When Corticosteroids Are Contraindicated

During ACTT-2, the median time to recovery was shorter in the baricitinib plus remdesivir arm (7 days) than in the placebo plus remdesivir arm (8 days) in the overall study population (rate ratio 1.16; 95% CI, 1.01–1.32; *P* = 0.03). In a subgroup analysis of participants who required high-flow oxygen or noninvasive ventilation (n = 216), the median time to recovery was 10 days in the baricitinib plus remdesivir arm and 18 days in the remdesivir alone arm (rate ratio 1.51; 95% CI, 1.10–2.08). There was no statistically significant difference in mortality by Day 28 between the baricitinib and placebo arms (OR 0.65; 95% CI, 0.39–1.09) in the overall population.

Baseline corticosteroid use was an exclusion criterion, and the trial enrolled most participants prior to the public release of RECOVERY data. It is unknown whether baricitinib would have an additive benefit to treatment with corticosteroids, or whether baricitinib is safer or more efficacious than corticosteroids. Because dexamethasone has been shown to reduce mortality in patients with COVID-19 who required supplemental oxygen, clinicians should prioritize the use of dexamethasone over the use of baricitinib in this group of patients. The Panel therefore reserves **baricitinib in combination with remdesivir** for the rare circumstance in which corticosteroids are contraindicated for this subgroup (**BIIa**). It is also unknown whether baricitinib would have additive benefit or adverse effects when given in combination with corticosteroids. Therefore, the Panel **recommends against** the use of a combination of **baricitinib, dexamethasone, and remdesivir**, except in a clinical trial (**BIII**).

For Hospitalized Patients With COVID-19 Who Require Invasive Mechanical Ventilation or Extracorporeal Membrane Oxygenation

Recommendations

- The Panel recommends the use of **dexamethasone** in hospitalized patients with COVID-19 who require invasive mechanical ventilation or ECMO (**AI**).

Additional Considerations

- If dexamethasone is not available, equivalent doses of alternative corticosteroids such as **prednisone**, **methylprednisolone**, or **hydrocortisone** may be used (**BIII**).
- For patients who initially received remdesivir monotherapy and progressed to requiring invasive mechanical ventilation or ECMO, dexamethasone should be initiated and remdesivir should be continued until the treatment course is completed.
- The Panel recommends against the use of remdesivir monotherapy (**AIIa**).

Rationale for the Use of Dexamethasone Monotherapy

As the disease progresses in patients with COVID-19, a systemic inflammatory response may lead to multiple organ dysfunction syndrome. The anti-inflammatory effects of corticosteroids mitigate the inflammatory response and have been associated with improved outcomes in people with COVID-19 and critical illness.

Dexamethasone reduces mortality in critically ill patients with COVID-19 according to a meta-analysis that aggregated seven randomized trials and included data on 1,703 critically ill patients.²¹ The largest trial in the meta-analysis was the RECOVERY trial, whose subgroup of mechanically ventilated patients was included.⁵ For details about the meta-analysis and the RECOVERY trial, see the [Corticosteroids](#) section. Because the benefits outweigh the potential harms, the Panel recommends the use of **dexamethasone** in hospitalized patients with COVID-19 who require invasive mechanical ventilation or ECMO (**AI**).

Considerations Related to the Use of Dexamethasone Plus Remdesivir Combination Therapy

Dexamethasone plus remdesivir combination therapy has not been evaluated in controlled studies; therefore, there is insufficient information to make a recommendation either for or against the use of this combination therapy. There is, however, a theoretical reason to administer dexamethasone plus remdesivir in patients who have recently been intubated. Antiviral therapy may prevent a steroid-related delay in viral clearance. This delay has been reported in the setting of other viral infections.^{13,14}

Some studies have suggested that corticosteroids slow SARS-CoV-2 clearance, but the studies to date are not definitive. For example, an observational study in people with non-severe COVID-19 suggested that viral clearance was delayed in patients who received corticosteroids,²² whereas a more recent study in patients with moderate to severe COVID-19 found no relationship between the use of corticosteroids and the rate of viral clearance.²⁰ Given the conflicting results from observational studies and the absence of clinical trial data, some Panel members would coadminister dexamethasone and remdesivir in patients who have recently been placed on mechanical ventilation (**CIII**) until more conclusive evidence becomes available, based on their concerns about delayed viral clearance in patients who received corticosteroids. Other Panel members would not coadminister these drugs due to uncertainties about the benefit of using remdesivir in critically ill patients described below.

Rationale for Recommending Against the Use of Remdesivir Monotherapy

A clear benefit of remdesivir monotherapy has not been demonstrated in patients who require invasive mechanical ventilation or ECMO. During ACTT-1, remdesivir did not improve the recovery rate in this subgroup of participants (recovery rate ratio 0.98; 95% CI, 0.70–1.36), and, in a post hoc analysis of deaths by Day 29, remdesivir also did not improve survival in this subgroup (HR 1.13, 95% CI, 0.67–1.89).¹ In the Solidarity trial, there was a trend toward increased mortality (rate ratio 1.27; 95% CI, 0.99–1.62) among patients who received mechanical ventilation and who were randomized to receive remdesivir rather than standard of care.¹² Taken together, these results do not demonstrate a clear benefit of remdesivir in critically ill patients.

For patients who start remdesivir monotherapy and then progress to requiring invasive mechanical ventilation or ECMO, the Panel recommends initiating dexamethasone and continuing remdesivir until the treatment course is completed. Clinical trials that evaluated remdesivir categorized patients based on their severity of illness at the start of treatment with remdesivir; therefore, patients may benefit from receiving remdesivir even if their clinical course progresses to a severity of illness for which the benefits of remdesivir are less certain.

References

1. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of COVID-19—final report. *N Engl J Med*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32445440>.
2. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet*. 2020;395(10236):1569-1578. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32423584>.
3. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. *JAMA*. 2020;324(11):1048-1057. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32821939>.
4. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 days in patients with severe COVID-19. *N Engl J Med*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32459919>.
5. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with COVID-19—preliminary report. *N Engl J Med*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32678530>.
6. Jeronimo CMP, Farias MEL, Val FFA, et al. Methylprednisolone as adjunctive therapy for patients hospitalized with COVID-19 (Metcovid): a randomised, double-blind, Phase IIb, placebo-controlled trial. *Clin Infect Dis*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32785710>.
7. Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: The CoDEX randomized clinical trial. *JAMA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32876695>.
8. Writing Committee for the R-CAP1, Angus DC, Derde L, et al. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: The REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. *JAMA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32876697>.
9. Chen P, Nirula A, Heller B, et al. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with COVID-19. *N Engl J Med*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33113295>.
10. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of casirivimab and imdevimab. 2020. Available at: <https://www.fda.gov/media/143892/download>. Accessed November 13, 2020.
11. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of bamlanivimab. 2020. Available at: <https://www.fda.gov/media/143603/download>. Accessed November 13, 2020.

12. 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>.
13. Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid therapy for critically ill patients with Middle East respiratory syndrome. *Am J Respir Crit Care Med*. 2018;197(6):757-767. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29161116>.
14. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Med*. 2006;3(9):e343. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16968120>.
15. Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, Lim WS. Corticosteroids as adjunctive therapy in the treatment of influenza. *Cochrane Database Syst Rev*. 2016;3:CD010406. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26950335>.
16. Chen Y, Li L. Influence of corticosteroid dose on viral shedding duration in patients with COVID-19. *Clin Infect Dis*. 2020. Available at: <https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa832/5863026>.
17. Li S, Hu Z, Song X. High-dose but not low-dose corticosteroids potentially delay viral shedding of patients with COVID-19. *Clin Infect Dis*. 2020. Available at: <https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa829/5863128>.
18. Ding C, Feng X, Chen Y, et al. Effect of corticosteroid therapy on the duration of SARS-CoV-2 clearance in patients with mild COVID-19: a retrospective cohort study. *Infect Dis Ther*. 2020;9(4):943-952. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32986226>.
19. Liu J, Zhang S, Dong X, et al. Corticosteroid treatment in severe COVID-19 patients with acute respiratory distress syndrome. *J Clin Invest*. 2020;130(12):6417-6428. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33141117>.
20. Spagnuolo V, Guffanti M, Galli L, et al. Viral clearance after early corticosteroid treatment in patients with moderate or severe covid-19. *Sci Rep*. 2020;10(1):21291. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33277573>.
21. WHO Rapid Evidence Appraisal for COVID-19 Therapies Working Group, Sterne JAC, Murthy S, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32876694>.
22. Li Q, Li W, Jin Y, et al. Efficacy evaluation of early, low-dose, short-term corticosteroids in adults hospitalized with non-severe COVID-19 pneumonia: a retrospective cohort study. *Infect Dis Ther*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32880102>.

Antiviral Drugs That Are Approved or Under Evaluation for the Treatment of COVID-19

Last Updated: February 11, 2021

Summary Recommendations
<p>Remdesivir is the only Food and Drug Administration-approved drug for the treatment of COVID-19. In this section, the COVID-19 Treatment Guidelines Panel (the Panel) provides recommendations for using antiviral drugs to treat COVID-19 based on the available data. As in the management of any disease, treatment decisions ultimately reside with the patient and their health care provider. For more information on these antiviral agents, see Table 2d.</p>
<p>Remdesivir</p> <ul style="list-style-type: none">See Therapeutic Management of Patients with COVID-19 for recommendations on using remdesivir with or without dexamethasone.
<p>Chloroquine or Hydroxychloroquine With or Without Azithromycin</p> <ul style="list-style-type: none">The Panel recommends against the use of chloroquine or hydroxychloroquine with or without azithromycin for the treatment of COVID-19 in hospitalized patients (AI).In nonhospitalized patients, the Panel recommends against the use of chloroquine or hydroxychloroquine with or without azithromycin for the treatment of COVID-19, except in a clinical trial (AIIa).The Panel recommends against the use of high-dose chloroquine (600 mg twice daily for 10 days) for the treatment of COVID-19 (AI).
<p>Lopinavir/Ritonavir and Other HIV Protease Inhibitors</p> <ul style="list-style-type: none">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).
<p>Ivermectin</p> <ul style="list-style-type: none">There are insufficient data for the Panel to recommend either for or against the use of ivermectin for the treatment of COVID-19. Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of ivermectin in the treatment of COVID-19.
<p>Rating of Recommendations: A = Strong; B = Moderate; C = Optional</p> <p>Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion</p>

Antiviral Therapy

Because severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication leads to many of the clinical manifestations of COVID-19, antiviral therapies are being investigated for the treatment of COVID-19. These drugs inhibit viral entry (via the angiotensin-converting enzyme 2 [ACE2] receptor and transmembrane serine protease 2 [TMPRSS2]), viral membrane fusion and endocytosis, or the activity of the SARS-CoV-2 3-chymotrypsin-like protease (3CLpro) and the RNA-dependent RNA polymerase.¹ Because viral replication may be particularly active early in the course of COVID-19, antiviral therapy may have the greatest impact before the illness progresses to the hyperinflammatory state that can characterize the later stages of disease, including critical illness.² For this reason, it is necessary to understand the role of antiviral medications in treating mild, moderate, severe, and critical illness in order to optimize treatment for people with COVID-19.

The following sections describe the underlying rationale for using different antiviral medications, provide the COVID-19 Treatment Guidelines Panel’s recommendations for using these medications to treat COVID-19, and summarize the existing clinical trial data. Additional antiviral therapies will be added to this section of the Guidelines as new evidence emerges.

References

1. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for Coronavirus Disease 2019 (COVID-19): a review. *JAMA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32282022>.
2. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. *J Heart Lung Transplant*. 2020;39(5):405-407. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32362390>.

Remdesivir

Last Updated: November 3, 2020

Remdesivir is an intravenous nucleotide prodrug of an adenosine analog. Remdesivir binds to the viral RNA-dependent RNA polymerase, inhibiting viral replication through premature termination of RNA transcription. It has demonstrated in vitro activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).¹ In a rhesus macaque model of SARS-CoV-2 infection, remdesivir treatment was initiated soon after inoculation; the remdesivir-treated animals had lower virus levels in the lungs and less lung damage than the control animals.²

Remdesivir is approved by the Food and Drug Administration (FDA) for the treatment of COVID-19 in hospitalized adult and pediatric patients (aged ≥ 12 years and weighing ≥ 40 kg). It is also available through an FDA Emergency Use Authorization (EUA) for the treatment of COVID-19 in hospitalized pediatric patients weighing 3.5 kg to < 40 kg or aged < 12 years and weighing ≥ 3.5 kg. Remdesivir should be administered in a hospital or a health care setting that can provide a similar level of care to an inpatient hospital.

Remdesivir has been studied in several clinical trials for the treatment of COVID-19. The recommendations from the COVID-19 Treatment Guidelines Panel (the Panel) are based on the results of these studies. See [Table 2a](#) for more information.

The safety and efficacy of combination therapy of remdesivir with corticosteroids have not been rigorously studied in clinical trials; however, there are theoretical reasons that the combination therapy may be beneficial in some patients with severe COVID-19. For the Panel's recommendations on using remdesivir with or without dexamethasone in certain hospitalized patients, see [Therapeutic Management of Patients with COVID-19](#).

Monitoring, Adverse Effects, and Drug-Drug Interactions

Remdesivir can cause gastrointestinal symptoms (e.g., nausea), elevated transaminase levels, an increase in prothrombin time, and hypersensitivity reactions.

Liver function tests and prothrombin time should be obtained in all patients before remdesivir is administered and during treatment as clinically indicated. Remdesivir may need to be discontinued if alanine transaminase (ALT) levels increase to > 10 times the upper limit of normal and should be discontinued if an increase in ALT level and signs or symptoms of liver inflammation are observed.³

Because the remdesivir formulation contains renally cleared sulfobutylether-beta-cyclodextrin sodium, patients with an estimated glomerular filtration rate (eGFR) of < 50 mL/minute were excluded from some clinical trials; other trials had an eGFR cutoff of < 30 mL/minute. Remdesivir **is not recommended** for patients with eGFR < 30 mL/minute. Renal function should be monitored in patients before and during remdesivir treatment as clinically indicated.³

Clinical drug-drug interaction studies of remdesivir have not been conducted. In vitro, remdesivir is a substrate of cytochrome P450 (CYP) 3A4 and of the drug transporters organic anion-transporting polypeptide (OATP) 1B1 and P-glycoprotein. It is also an inhibitor of CYP3A4, OATP1B1, OATP1B3, and MATE1.³

Minimal to no reduction in remdesivir exposure is expected when remdesivir is coadministered with dexamethasone, according to information provided by Gilead Sciences (written communication, July 2020). Chloroquine or hydroxychloroquine may decrease the antiviral activity of remdesivir;

coadministration of these drugs **is not recommended**.³ Remdesivir is not expected to have any significant interactions with oseltamivir or baloxavir, according to information provided by Gilead Sciences (written communications, August and September 2020).

See [Table 2d](#) for more information.

Considerations in Pregnancy

- Pregnant patients were excluded from the clinical trials that evaluated the safety and efficacy of remdesivir for the treatment of COVID-19, but preliminary reports of use in pregnant patients through the remdesivir compassionate use program are reassuring.
- Among 86 pregnant and postpartum hospitalized patients with severe COVID-19 who received compassionate use remdesivir, the therapy was well tolerated, with a low rate of serious adverse events.⁴
- Remdesivir should not be withheld from pregnant patients if it is otherwise indicated.

Considerations in Children

- The safety and effectiveness of remdesivir for the treatment of COVID-19 have not been evaluated in pediatric patients aged <12 years or weighing <40 kg.
- Remdesivir is available through an FDA EUA for the treatment of COVID-19 in hospitalized pediatric patients weighing 3.5 kg to <40 kg or aged <12 years and weighing ≥3.5 kg.
- A clinical trial is currently evaluating the pharmacokinetics of remdesivir in children (*ClinicalTrials.gov* identifier [NCT04431453](#)).

Clinical Trials

Several clinical trials that are evaluating remdesivir for the treatment of COVID-19 are currently underway or in development. Please see [ClinicalTrials.gov](#) for the latest information.

References

1. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*. 2020;30(3):269-271. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32020029>.
2. Williamson BN, Feldmann F, Schwarz B, et al. Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. *Nature*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32516797>.
3. Remdesivir (VEKLURY) [package insert]. Food and Drug Administration. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/214787Orig1s000lbl.pdf. Accessed: October 25, 2020.
4. Burwick RM, Yawetz S, Stephenson KE, et al. Compassionate use of remdesivir in pregnant women with severe Covid-19. *Clin Infect Dis*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33031500>.

Table 2a. Remdesivir: Selected Clinical Data

Last Updated: February 11, 2021

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

Study Design	Methods	Results	Limitations and Interpretation
Adaptive COVID-19 Treatment Trial (ACTT-1)¹			
Multinational, placebo-controlled, double-blind RCT in hospitalized patients (n = 1,062)	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged ≥18 years • Laboratory-confirmed SARS-CoV-2 infection • At least 1 of the following conditions: <ul style="list-style-type: none"> • Pulmonary infiltrates, as determined by radiographic imaging • SpO₂ ≤94% on room air • Required supplemental oxygen • Required mechanical ventilation • Required ECMO <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • ALT or AST >5 times ULN • eGFR <30 mL/min • Pregnancy or breastfeeding <p>Interventions:</p> <ul style="list-style-type: none"> • IV RDV 200 mg on Day 1, then 100 mg daily for up to 9 more days • Placebo for 10 days <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Time to clinical recovery <p>Ordinal Scale Definitions:</p> <ol style="list-style-type: none"> 1. Not hospitalized, no limitations 2. Not hospitalized, with limitations 3. Hospitalized, no active medical problems 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • RDV (n = 541) and placebo (n = 521) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Median time from symptom onset to randomization was 9 days (IQR 6–12 days). <p>Outcomes</p> <p><i>Overall Results:</i></p> <ul style="list-style-type: none"> • RDV reduced time to recovery compared to placebo (10 days vs. 15 days; RRR 1.29; 95% CI, 1.12–1.49; <i>P</i> < 0.001). • Clinical improvement based on ordinal scale was higher at Day 15 in RDV arm (OR 1.5; 95% CI, 1.2–1.9; <i>P</i> < 0.001). • No statistically significant difference in mortality by Day 29 between RDV and placebo arms (HR 0.73; 95% CI, 0.52–1.03; <i>P</i> = 0.07). • Benefit of RDV was greatest in patients randomized during the first 10 days after symptom onset. <p><i>Results by Disease Severity at Enrollment:</i></p> <ul style="list-style-type: none"> • No difference in median time to recovery between arms among patients who had mild to moderate disease at enrollment. • Benefit of RDV for reducing time to recovery was clearest in patients who required supplemental oxygenation at enrollment (n = 435; RRR 1.45; 95% CI, 1.18–1.79), and RDV appeared to confer 	<p>Limitations:</p> <ul style="list-style-type: none"> • Wide range of disease severity; study was not powered to detect differences within subgroups • Powered to detect differences in clinical improvement, not mortality • No data collected on longer-term morbidity <p>Interpretation:</p> <ul style="list-style-type: none"> • In patients with severe COVID-19, RDV reduced time to clinical recovery. • Benefit of RDV was most apparent in hospitalized patients on supplemental oxygen. • No observed benefit in those on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO, but the study was not powered to detect differences within subgroups. • No observed benefit of RDV in patients with mild or moderate COVID-19, but the number of participants in these categories was relatively small.

Study Design	Methods	Results	Limitations and Interpretation
Adaptive COVID-19 Treatment Trial (ACTT-1)¹, continued			
	4. Hospitalized, not on oxygen 5. Hospitalized, on oxygen 6. Hospitalized, on high-flow oxygen or noninvasive mechanical ventilation 7. Hospitalized, on mechanical ventilation or ECMO 8. Death	a survival benefit in this subgroup (HR for death by Day 29 0.30; 95% CI, 0.14–0.64). <ul style="list-style-type: none"> • No observed difference in time to recovery between arms in patients on high-flow oxygen or noninvasive ventilation at enrollment (RRR 1.09; 95% CI, 0.76–1.57). No evidence that RDV affected mortality rate in this subgroup (HR 1.02; 95% CI, 0.54–1.91). • No observed difference in time to recovery between arms in patients on mechanical ventilation or ECMO at enrollment (RRR 0.98; 95% CI, 0.70–1.36). No evidence that RDV affected mortality rate in this subgroup (HR 1.13; 95% CI, 0.67–1.89). <i>Safety Results:</i> <ul style="list-style-type: none"> • Percentages of patients with SAEs were similar between arms (25% vs. 32%). • Transaminase elevations: 6% of RDV recipients, 10.7% of placebo recipients 	
Remdesivir Versus Placebo for Severe COVID-19 in China²			
Multicenter, placebo-controlled, double-blind RCT in hospitalized patients with severe COVID-19 (n = 237)	Key Inclusion Criteria: <ul style="list-style-type: none"> • Aged ≥18 years • Laboratory-confirmed SARS-CoV-2 infection • Time from symptom onset to randomization <12 days • SpO₂ ≤94% on room air or PaO₂/FiO₂ <300 mm Hg • Radiographically confirmed pneumonia Key Exclusion Criteria: <ul style="list-style-type: none"> • ALT or AST >5 times ULN • eGFR <30 mL/min • Pregnancy or breastfeeding 	Number of Participants: <ul style="list-style-type: none"> • ITT analysis: RDV (n = 158) and placebo (n = 78) • Study stopped before reaching target enrollment of 453 patients due to control of the COVID-19 outbreak in China. Participant Characteristics: <ul style="list-style-type: none"> • Median time from symptom onset to randomization: 9 days for RDV arm, 10 days for placebo arm • Receipt of corticosteroids: 65% of patients in RDV arm, 68% in placebo arm • Receipt of LPV/RTV: 28% of patients in RDV arm, 29% in placebo arm 	Limitations: <ul style="list-style-type: none"> • Sample size did not have sufficient power to detect differences in clinical outcomes. • Use of concomitant medications (i.e., corticosteroids, LPV/RTV, IFNs) may have obscured effects of RDV. Interpretation: <ul style="list-style-type: none"> • No difference in time to clinical improvement, 28-day mortality, or rate of SARS-CoV-2 clearance between RDV-treated and placebo-treated patients;

Study Design	Methods	Results	Limitations and Interpretation
Remdesivir Versus Placebo for Severe COVID-19 in China², continued			
	<p>Interventions:</p> <ul style="list-style-type: none"> • IV RDV 200 mg on Day 1, then 100 mg daily for 9 days • Saline placebo for 10 days <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Time to clinical improvement, defined as improvement on an ordinal scale or being discharged alive from the hospital 	<ul style="list-style-type: none"> • Receipt of IFN alfa-2b: 29% of patients in RDV arm, 38% in placebo arm <p>Outcomes:</p> <ul style="list-style-type: none"> • No difference in time to clinical improvement between RDV and placebo arms (median time 21 days vs. 23 days; HR 1.23; 95% CI, 0.87–1.75). • For patients who started RDV or placebo within 10 days of symptom onset, faster time to clinical improvement was seen with RDV (median time 18 days vs. 23 days; HR 1.52; 95% CI, 0.95–2.43); however, this was not statistically significant. • 28-day mortality was similar between arms (14% of patients in RDV arm, 13% in placebo arm). • No difference between arms in SARS-CoV-2 viral load at baseline, and rate of decline over time was similar. • Percentage of patients with AEs: 66% in RDV arm, 64% in placebo arm • Discontinuations due to AEs: 12% of patients in RDV arm, 5% in placebo arm 	<p>however, study was underpowered to detect differences in these outcomes between arms.</p>
World Health Organization Solidarity Trial³			
<p>International, open-label, adaptive RCT with multiple treatment arms that enrolled hospitalized patients with COVID-19 (n = 11,330). In 1 arm, patients received RDV.</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged ≥ 18 years • Not known to have received any study drug • Not expected to be transferred elsewhere within 72 hours • Physician reported no contraindications to study drugs <p>Interventions:</p> <ul style="list-style-type: none"> • IV RDV 200 mg on Day 0, then 100 mg daily on Days 1–9 • Local SOC 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • ITT analysis: RDV (n = 2,743) and SOC (n = 2,708) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Percentage of patients aged 50–69 years: 47% in RDV arm, 48% in SOC arm • Percentage of patients aged ≥ 70 years: 18% in RDV arm, 17% in SOC arm • 67% of patients in both arms were on supplemental oxygen at entry. • 9% of patients in both arms were mechanically ventilated at entry. 	<p>Limitations:</p> <ul style="list-style-type: none"> • Open-label study design limits the ability to assess time to recovery; clinicians and patients were aware of treatment assignment, so RDV may have been continued to complete the treatment course even if the patient had improved. • No data on time from symptom onset to enrollment • No assessment of outcomes post hospital discharge

Study Design	Methods	Results	Limitations and Interpretation
World Health Organization Solidarity Trial³, continued			
	<p>Primary Endpoint:</p> <ul style="list-style-type: none"> In-hospital mortality <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> Initiation of mechanical ventilation Duration of hospitalization 	<ul style="list-style-type: none"> Percentage of patients hospitalized for ≥ 2 days at entry: 40% in RDV arm, 39% in SOC arm Percentages of patients with comorbid conditions were similar between RDV and SOC arms: diabetes (26% and 25%), heart disease (21% both groups), and chronic lung disease (6% and 5%). 48% of patients in both arms received corticosteroids. <p>Primary Outcomes:</p> <ul style="list-style-type: none"> In-hospital mortality: 301 deaths (11.0%) in RDV arm, 303 deaths (11.2%) in SOC arm Rate ratios for in-hospital death: <ul style="list-style-type: none"> Overall: 0.95 (95% CI, 0.81–1.11) No mechanical ventilation at entry: 0.86 (99% CI, 0.67–1.11) Mechanical ventilation at entry: 1.20 (99% CI, 0.80–1.80) <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> Initiation of mechanical ventilation: 295 patients (10.8%) in RDV arm, 284 patients (10.5%) in SOC arm 	<p>Interpretation:</p> <ul style="list-style-type: none"> RDV did not decrease in-hospital mortality in hospitalized patients when compared to local SOC.
Remdesivir Versus Standard of Care in Hospitalized Patients with Moderate COVID-19⁴			
Open-label randomized trial in hospitalized patients (n = 596)	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> Laboratory-confirmed SARS-CoV-2 infection Moderate pneumonia, defined as radiographic evidence of pulmonary infiltrates and SpO₂ >94% on room air <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> ALT or AST >5 times ULN CrCl <50 mL/min 	<p>Number of Participants:</p> <ul style="list-style-type: none"> 584 patients began treatment: 10-day RDV (n = 193), 5-day RDV (n = 191), and SOC (n = 200) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> Demographic and baseline disease characteristics were similar across all arms. <p>Outcomes:</p> <ul style="list-style-type: none"> 5-day RDV had significantly higher odds of better clinical status distribution on Day 11 than SOC (OR 1.65; 95% CI, 1.09–2.48; <i>P</i> = 0.02). 	<p>Limitations:</p> <ul style="list-style-type: none"> Open-label design may have affected decisions related to concomitant medication use and hospital discharge. Greater proportion of patients in SOC arm received HCQ, LPV/RTV, or AZM, which may cause AEs and have not shown clinical benefits in hospitalized patients with COVID-19.

Study Design	Methods	Results	Limitations and Interpretation
Remdesivir Versus Standard of Care in Hospitalized Patients with Moderate COVID-19⁴, continued			
	<p>Interventions:</p> <ul style="list-style-type: none"> • IV RDV 200 mg on Day 1, then 100 mg daily for 9 days • IV RDV 200 mg on Day 1, then 100 mg daily for 4 days • Local SOC <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Clinical status on Day 11, as measured by a 7-point ordinal scale 	<ul style="list-style-type: none"> • Clinical status distribution on Day 11 was not significantly different between the 10-day RDV and SOC arms ($P = 0.18$). • By Day 28, there were more hospital discharges among patients who received RDV (89% in 5-day arm and 90% in 10-day arm) than those who received SOC (83%). • Mortality was low in all arms (1% to 2%). • Percentages of patients with AEs in RDV arms vs. SOC arm: nausea (10% vs. 3%), hypokalemia (6% vs. 2%), and headache (5% vs. 3%) 	<ul style="list-style-type: none"> • No data on time to return to activity for discharged patients <p>Interpretation:</p> <ul style="list-style-type: none"> • Hospitalized patients with moderate COVID-19 who received 5 days of RDV had better outcomes than those who received SOC; however, difference between arms was of uncertain clinical importance.
Different Durations of Remdesivir Treatment in Hospitalized Patients⁵			
<p>Manufacturer-sponsored, multinational, randomized, open-label trial in hospitalized patients with COVID-19 (n = 402)</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged ≥ 12 years • Laboratory-confirmed SARS-CoV-2 infection • Radiographic evidence of pulmonary infiltrates • SpO₂ $\leq 94\%$ on room air or receipt of supplemental oxygen <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Receipt of mechanical ventilation or ECMO • Multiorgan failure • ALT or AST >5 times ULN • Estimated CrCl <50 mL/min <p>Interventions:</p> <ul style="list-style-type: none"> • IV RDV 200 mg on Day 1, then 100 mg daily for 4 days • IV RDV 200 mg on Day 1, then 100 mg daily for 9 days <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Clinical status at Day 14, as measured by a 7-point ordinal scale 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • 397 participants began treatment: 5-day RDV (n = 200) and 10-day RDV (n = 197) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • At baseline, patients in 10-day arm had worse clinical status (based on ordinal scale distribution) than those in 5-day arm ($P = 0.02$) <p>Outcomes:</p> <ul style="list-style-type: none"> • After adjusting for imbalances in baseline clinical status, Day 14 distribution in clinical status on the ordinal scale was similar between arms ($P = 0.14$). • Time to achieve clinical improvement of at least 2 levels on the ordinal scale (median day of 50% cumulative incidence) was similar between arms (10 days vs. 11 days). • Median durations of hospitalization among patients discharged on or before Day 14 were similar between 5-day (7 days; IQR 6–10 days) and 10-day arms (8 days; IQR 5–10 days). • Percentages of patients with SAEs: 35% in 10-day arm, 21% in 5-day arm 	<p>Limitations:</p> <ul style="list-style-type: none"> • This was an open-label trial without a placebo control arm, so clinical benefit of RDV (compared with no RDV) could not be assessed. • There were baseline imbalances in clinical status of patients in the 5-day and 10-day arms. <p>Interpretation:</p> <ul style="list-style-type: none"> • In hospitalized patients with severe COVID-19 who were not on mechanical ventilation or ECMO, RDV treatment for 5 or 10 days had a similar clinical benefit.

Study Design	Methods	Results	Limitations and Interpretation
Different Durations of Remdesivir Treatment in Hospitalized Patients⁵ , continued			
		• Discontinuations due to AEs: 4% of patients in 5-day arm, 10% in 10-day arm	

Key: AE = adverse effects; ALT = alanine transaminase; AST = aspartate aminotransferase; AZM = azithromycin; CrCl = creatinine clearance; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; HCQ = hydroxychloroquine; IFN = interferon; ITT = intention to treat; IV = intravenous; LPV/RTV = lopinavir/ritonavir; the Panel = the COVID-19 Treatment Guidelines Panel; PaO₂/FiO₂ = ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; RCT = randomized controlled trial; RDV = remdesivir; RRR = recovery rate ratio; SAE = serious adverse effects; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOC = standard of care; SpO₂ = saturation of oxygen; ULN = upper limit of normal

References

1. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of COVID-19—final report. *N Engl J Med*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32445440>.
2. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet*. 2020;395(10236):1569-1578. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32423584>.
3. 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>.
4. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. *JAMA*. 2020;324(11):1048-1057. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32821939>.
5. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 days in patients with severe COVID-19. *N Engl J Med*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32459919>.

Chloroquine or Hydroxychloroquine With or Without Azithromycin

Last Updated: October 9, 2020

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 (SLE) and rheumatoid arthritis, in addition to malaria. In general, hydroxychloroquine has fewer and less severe toxicities (including less propensity to prolong the QTc interval) and fewer drug-drug interactions than chloroquine.

Both chloroquine and hydroxychloroquine increase the endosomal pH, inhibiting fusion of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the host cell membranes.¹ Chloroquine inhibits glycosylation of the cellular angiotensin-converting enzyme 2 receptor, which may interfere with binding of severe acute respiratory syndrome-associated coronavirus (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. It has been hypothesized that these effects are other potential mechanisms of action for the treatment of COVID-19. However, despite demonstrating antiviral activity in some in vitro systems, hydroxychloroquine with or without azithromycin did not reduce upper or lower respiratory tract viral loads or demonstrate clinical efficacy in a rhesus macaque model.⁴

Chloroquine and hydroxychloroquine, with or without azithromycin, have been studied in multiple clinical trials for the treatment of COVID-19. The recommendations below are based on an assessment of the collective evidence from these studies.

Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of **chloroquine** or **hydroxychloroquine** with or without **azithromycin** for the treatment of COVID-19 in hospitalized patients (**AI**).
- In nonhospitalized patients, the Panel **recommends against** the use of **chloroquine** or **hydroxychloroquine** with or without **azithromycin** for the treatment of COVID-19, except in a clinical trial (**AIIa**).
- The Panel **recommends against** the use of **high-dose chloroquine** (600 mg twice daily for 10 days) for the treatment of COVID-19 (**AI**).

Rationale

The safety and efficacy of chloroquine and hydroxychloroquine with or without azithromycin have been evaluated in randomized clinical trials, observational studies, and single-arm studies. Please see [Table 2b](#) for more information.

In a large randomized controlled trial of hospitalized patients in the United Kingdom, hydroxychloroquine did not decrease 28-day mortality when compared to the usual standard of care. Participants 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.⁵

In another randomized controlled trial that was conducted in Brazil, neither hydroxychloroquine alone nor hydroxychloroquine plus azithromycin improved clinical outcomes among hospitalized patients with mild to moderate COVID-19. More adverse events occurred among patients who received hydroxychloroquine or hydroxychloroquine plus azithromycin than among those who received the standard of care.⁶ Data from another randomized study of hospitalized patients with severe COVID-19 do not support using hydroxychloroquine plus azithromycin over hydroxychloroquine alone.⁷

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. For example, in a large retrospective observational study of patients who were hospitalized with COVID-19, hydroxychloroquine use was not associated with a reduced risk of death or mechanical ventilation.⁸ Another multicenter retrospective observational study evaluated the use of hydroxychloroquine with and without azithromycin in a random sample of a large cohort of hospitalized patients with COVID-19.⁹ Patients who received hydroxychloroquine with or without azithromycin did not have a decreased risk of in-hospital mortality when compared to those who received neither hydroxychloroquine nor azithromycin.

Conversely, a large retrospective cohort study reported a survival benefit among hospitalized patients who received either hydroxychloroquine alone or hydroxychloroquine plus azithromycin, compared to those who received neither drug.¹⁰ However, patients who did not receive hydroxychloroquine had a lower rate of admission to the intensive care unit, which suggests that patients in this group may have received less-aggressive care. Furthermore, a substantially higher percentage of patients in the hydroxychloroquine arms also received corticosteroids (77.1% of patients in the hydroxychloroquine arms vs. 36.5% of patients in the control arm). Given that the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial showed that corticosteroids improve the survival rate of patients with COVID-19 (see [Corticosteroids](#)), it is possible that the findings in this study were confounded by this imbalance in corticosteroid use.¹¹ These and other observational and single-arm studies are summarized in [Table 2b](#).

Many of the observational studies that have evaluated the use of chloroquine or hydroxychloroquine in patients with COVID-19 have attempted to control for confounding variables. However, study arms may be unbalanced in some of these studies, and some studies may not account for all potential confounding factors. These factors limit the ability to interpret and generalize the results from observational studies; therefore, results from these studies are not as definitive as those from large randomized trials. Given the lack of a benefit seen in the randomized clinical trials and the potential for toxicity, the Panel **recommends against** using hydroxychloroquine or chloroquine with or without azithromycin to treat COVID-19 in hospitalized patients (**AI**).

The Panel also **recommends against** using high-dose chloroquine to treat COVID-19 (**AI**). High-dose chloroquine (600 mg twice daily for 10 days) has been associated with more severe toxicities than lower-dose chloroquine (450 mg twice daily for 1 day, followed by 450 mg once daily for 4 days). A randomized clinical trial compared the use of high-dose chloroquine and low-dose chloroquine in hospitalized patients with severe COVID-19. In addition, all participants received azithromycin, and 89% of the participants received oseltamivir. The study was discontinued early when preliminary results showed higher rates of mortality and QTc prolongation in the high-dose chloroquine group.¹²

Several randomized trials have not shown a clinical benefit for hydroxychloroquine in nonhospitalized patients with COVID-19. However, other clinical trials are still ongoing.^{13,14} In nonhospitalized patients, the Panel **recommends against** the use of chloroquine or hydroxychloroquine with or without azithromycin for the treatment of COVID-19, except in a clinical trial (**AI**).

The combination of hydroxychloroquine and azithromycin is associated with QTc prolongation in patients with COVID-19. Given the long half-lives of both azithromycin (up to 72 hours) and hydroxychloroquine (up to 40 days), caution is warranted even when the two drugs are used sequentially instead of concomitantly.¹⁵

Please see [Table 2b](#) for additional details.

Adverse Effects

Chloroquine and hydroxychloroquine have a similar toxicity profile, although hydroxychloroquine is better tolerated and has a lower incidence of toxicity than chloroquine.

Cardiac Adverse Effects

- QTc prolongation, Torsade de Pointes, ventricular arrhythmia, and cardiac deaths.¹⁶ If chloroquine or hydroxychloroquine is used, clinicians should monitor the patient for adverse events, especially prolonged QTc interval (**AIII**).
- The risk of QTc prolongation is greater for chloroquine than for hydroxychloroquine.
- Concomitant medications that pose a moderate to high risk for QTc prolongation (e.g., antiarrhythmics, antipsychotics, antifungals, macrolides [including azithromycin],¹⁶ fluoroquinolone antibiotics)¹⁷ should be used only if necessary. Consider using doxycycline rather than azithromycin as empiric therapy for atypical pneumonia.
- Multiple studies have demonstrated that concomitant use of hydroxychloroquine and azithromycin can prolong the QTc interval;¹⁸⁻²⁰ in an observational study, the use of hydroxychloroquine plus azithromycin was associated with increased odds of cardiac arrest.⁹ The use of this combination warrants careful monitoring.
- Baseline and follow-up electrocardiograms are recommended when there are potential drug interactions with concomitant medications (e.g., azithromycin) or underlying cardiac diseases.²¹
- The risk-benefit ratio should be assessed for patients with cardiac disease, a history of ventricular arrhythmia, bradycardia (<50 bpm), or uncorrected hypokalemia and/or hypomagnesemia.

Other Adverse Effects

- Hypoglycemia, rash, and nausea. Divided doses may reduce nausea.
- Retinopathy. Bone marrow suppression may occur with long-term use, but this is not likely with short-term use.

Drug-Drug Interactions

Chloroquine and hydroxychloroquine are moderate inhibitors of cytochrome P450 (CYP) 2D6, and these drugs are also P-glycoprotein (P-gp) inhibitors. Use caution when administering these drugs with medications that are metabolized by CYP2D6 (e.g., certain antipsychotics, beta-blockers, selective serotonin reuptake inhibitors, methadone) or transported by P-gp (e.g., certain direct-acting oral anticoagulants, digoxin).²² Chloroquine and hydroxychloroquine may decrease the antiviral activity of remdesivir; coadministration of these drugs **is not recommended**.²³

Considerations in Pregnancy

- Antirheumatic doses of chloroquine and hydroxychloroquine have been used safely in pregnant women with SLE.

- Hydroxychloroquine exposure has not been associated with adverse pregnancy outcomes in ≥ 300 human pregnancies.
- A lower dose of chloroquine (500 mg once a week) is used for malaria prophylaxis during pregnancy.
- No dose changes are necessary for chloroquine or hydroxychloroquine during pregnancy.

Considerations in Children

- Chloroquine and hydroxychloroquine have been routinely used in pediatric populations for the treatment and prevention of malaria and for rheumatologic conditions.

Drug Availability

- Hydroxychloroquine, chloroquine, and azithromycin **are not approved** by the Food and Drug Administration (FDA) for the treatment of COVID-19.
- Hydroxychloroquine is approved by the FDA for the treatment of malaria, lupus erythematosus, and rheumatoid arthritis. Chloroquine is approved for the treatment of malaria and extraintestinal amebiasis. Azithromycin is commonly used for the treatment and/or prevention of nontuberculous mycobacterial infection, various sexually transmitted infections, and various bacterial infections.

References

1. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res.* 2020;30(3):269-271. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32020029>.
2. Vincent MJ, Bergeron E, Benjannet S, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. *Virology.* 2005;2:69. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16115318>.
3. Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov.* 2020;6:16. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32194981>.
4. Maisonnasse P, Guedj J, Contreras V, et al. Hydroxychloroquine use against SARS-CoV-2 infection in non-human primates. *Nature.* 2020;585(7826):584-587. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32698191>.
5. Horby P, Mafham M, Linsell L, et al. Effect of hydroxychloroquine in hospitalized patients with COVID-19: preliminary results from a multi-centre, randomized, controlled trial. *medRxiv.* 2020;Preprint. Available at: <https://www.medrxiv.org/content/10.1101/2020.07.15.20151852v1>.
6. Cavalcanti AB, Zampieri FG, Rosa RG, et al. Hydroxychloroquine with or without azithromycin in mild-to-moderate COVID-19. *N Engl J Med.* 2020; Published online ahead of print. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32706953>.
7. Furtado RHM, Berwanger O, Fonseca HA, et al. Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial. *Lancet.* 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32896292>.
8. Geleris J, Sun Y, Platt J, et al. Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19. *N Engl J Med.* 2020; Published online ahead of print. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32379955>.
9. Rosenberg ES, Dufort EM, Udo T, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York state. *JAMA.* 2020;323(24):2493-2502. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32392282>.

10. Arshad S, Kilgore P, Chaudhry ZS, et al. Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. *Int J Infect Dis.* 2020;97:396-403. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32623082>.
11. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with COVID-19—preliminary report. *N Engl J Med.* 2020; Published online ahead of print. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32678530>.
12. Borba MGS, Val FFA, Sampaio VS, et al. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial. *JAMA Netw Open.* 2020;3(4):e208857. Available at: <https://pubmed.ncbi.nlm.nih.gov/32330277/>.
13. Skipper CP, Pastick KA, Engen NW, et al. Hydroxychloroquine in nonhospitalized adults with early COVID-19: a randomized trial. *Ann Intern Med.* 2020; Published online ahead of print. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32673060>.
14. Mitja O, Corbacho-Monne M, Ubals M, et al. Hydroxychloroquine for early treatment of adults with mild COVID-19: a randomized-controlled trial. *Clin Infect Dis.* 2020; Published online ahead of print. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32674126>.
15. Institute for Safe Medication Practices. Special Edition: Medication Safety Alert! 2020. Available at: <https://ismp.org/acute-care/special-edition-medication-safety-alert-april-9-2020/covid-19>. Accessed September 24, 2020.
16. Nguyen LS, Dolladille C, Drici MD, et al. Cardiovascular toxicities associated with hydroxychloroquine and azithromycin: an analysis of the World Health Organization pharmacovigilance database. *Circulation.* 2020;142(3):303-305. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32442023>.
17. CredibleMeds. Combined list of drugs that prolong QT and/or cause torsades de pointes (TDP). 2020. Available at: <https://crediblemeds.org/pdftemp/pdf/CombinedList.pdf>.
18. Chorin E, Dai M, Shulman E, et al. The QT interval in patients with COVID-19 treated with hydroxychloroquine and azithromycin. *Nature Medicine.* 2020. Available at: <https://doi.org/10.1038/s41591-020-0888-2>.
19. Mercurio NJ, Yen CF, Shim DJ, et al. Risk of QT interval prolongation associated with use of hydroxychloroquine with or without concomitant azithromycin among hospitalized patients testing positive for coronavirus disease 2019 (COVID-19). *JAMA Cardiol.* 2020;5(9):1036-1041. Available at: <https://pubmed.ncbi.nlm.nih.gov/32936252/>.
20. Bessiere F, Rocchia H, Deliniere A, et al. Assessment of QT intervals in a case series of patients with coronavirus disease 2019 (COVID-19) Infection treated with hydroxychloroquine alone or in combination with azithromycin in an intensive care unit. *JAMA Cardiol.* 2020;5(9):1067-1069. Available at: <https://pubmed.ncbi.nlm.nih.gov/32936266/>.
21. American College of Cardiology. Ventricular arrhythmia risk due to hydroxychloroquine-azithromycin treatment for COVID-19. 2020. Available at: <https://www.acc.org/latest-in-cardiology/articles/2020/03/27/14/00/ventricular-arrhythmia-risk-due-to-hydroxychloroquine-azithromycin-treatment-for-covid-19>. Accessed September 24, 2020.
22. University of Liverpool. COVID-19 drug interactions. 2020. Available at: <https://www.covid19-druginteractions.org/>. Accessed September 24, 2020.
23. Food and Drug Administration. Remdesivir by Gilead Sciences: FDA warns of newly discovered potential drug interaction that may reduce effectiveness of treatment. 2020. Available at: <https://www.fda.gov/safety/medical-product-safety-information/remdesivir-gilead-sciences-fda-warns-newly-discovered-potential-drug-interaction-may-reduce>. Accessed July 2, 2020.

Table 2b. Chloroquine or Hydroxychloroquine With or Without Azithromycin: Selected Clinical Data

Last Updated: October 9, 2020

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 [ClinicalTrials.gov](https://www.clinicaltrials.gov) for more information on clinical trials that are evaluating CQ, HCQ, and AZM.

The Panel has reviewed other clinical studies of HCQ with or without AZM and studies of CQ for the treatment of COVID-19.¹⁻¹¹ 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 [archived versions](#) of the COVID-19 Treatment Guidelines.

Study Design	Methods	Results	Limitations and Interpretation
Randomised Evaluation of COVID-19 Therapy (RECOVERY) Trial¹²			
<p>Open-label RCT with multiple arms, including a control arm; in 1 arm, hospitalized patients received HCQ (n = 11,197)</p> <p><i>This is a preliminary report that has not yet been peer reviewed.</i></p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> Clinically suspected or laboratory-confirmed SARS-CoV-2 infection <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> Patients with prolonged QTc intervals were excluded from HCQ arm. <p>Interventions:</p> <ul style="list-style-type: none"> HCQ 800 mg at entry and at 6 hours, then HCQ 400 mg every 12 hours for 9 days or until discharge Usual SOC <p>Primary Endpoint:</p> <ul style="list-style-type: none"> All-cause mortality at Day 28 after randomization 	<p>Number of Participants:</p> <ul style="list-style-type: none"> HCQ (n = 1,561) and SOC (n = 3,155) Study enrollment ended early after investigators and trial-steering committee concluded that the data showed no benefit for HCQ. <p>Participant Characteristics:</p> <ul style="list-style-type: none"> 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 invasive mechanical ventilation 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. 	<p>Limitations:</p> <ul style="list-style-type: none"> Not blinded Information on occurrence of new major cardiac arrhythmia was not collected throughout the trial. <p>Interpretation:</p> <ul style="list-style-type: none"> 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 invasive mechanical ventilation 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
Randomised Evaluation of COVID-19 Therapy (RECOVERY) Trial¹², continued			
		<p>Outcomes:</p> <ul style="list-style-type: none"> • No significant difference in 28-day mortality between the 2 arms; 418 patients (26.8%) in HCQ arm and 788 patients (25.0%) in SOC arm had died by Day 28 (RR 1.09; 95% CI, 0.96–1.23; <i>P</i> = 0.18). • A similar 28-day mortality for HCQ patients was reported during the post hoc exploratory analysis that was restricted to the 4,234 participants (90%) 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 invasive mechanical ventilation 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 698 patients (44.7%) in HCQ arm and 1,357 patients (43.0%) 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. 	
Hydroxychloroquine and Hydroxychloroquine Plus Azithromycin for Mild or Moderate COVID-19¹³			
Open-label, 3-arm RCT in hospitalized patients (n = 667)	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged ≥18 years • Clinically suspected or laboratory-confirmed SARS-CoV-2 infection • Mild or moderate COVID-19 • Duration of symptoms ≤14 days 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • Modified ITT analysis included patients with laboratory-confirmed SARS-CoV-2 infection (n = 504). <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Mean age was 50 years. • 58% of patients were men. • 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. 	<p>Limitations:</p> <ul style="list-style-type: none"> • Not blinded • Follow-up period was restricted to 15 days. <p>Interpretation:</p> <ul style="list-style-type: none"> • Neither HCQ alone nor HCQ plus AZM improved clinical outcomes at Day 15 after randomization among hospitalized patients with mild or moderate COVID-19.

Study Design	Methods	Results	Limitations and Interpretation
Hydroxychloroquine and Hydroxychloroquine Plus Azithromycin for Mild or Moderate COVID-19¹³, continued			
	<p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Need for >4 L of supplemental oxygen or $\geq 40\%$ FiO₂ by face mask • History of ventricular tachycardia • QT interval ≥ 480 ms <p>Interventions:</p> <ul style="list-style-type: none"> • 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 <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Clinical status at Day 15, as assessed by a 7-point ordinal scale among the patients with confirmed SARS-CoV-2 infection <p>Ordinal Scale Definitions:</p> <ol style="list-style-type: none"> 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 	<ul style="list-style-type: none"> • 23.3% to 23.9% of patients received oseltamivir. <p>Outcomes:</p> <ul style="list-style-type: none"> • No significant difference between the odds of worse clinical status at Day 15 for patients in HCQ arm (OR 1.21; 95% CI, 0.69–2.11; $P = 1.00$) and patients in HCQ plus AZM arm (OR 0.99; 95% CI, 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%). • 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 Versus Standard of Care for Mild or Moderate COVID-19¹⁴			
<p>Multicenter, randomized, open-label trial (n = 150)</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged ≥18 years • Laboratory-confirmed SARS-CoV-2 infection <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Severe conditions, including heart, liver, or kidney disease • Inability to take oral medications • Pregnancy or breastfeeding <p>Interventions:</p> <ul style="list-style-type: none"> • HCQ 1,200 mg once daily for 3 days, then HCQ 800 mg once daily for 2 weeks (in patients with mild or moderate COVID-19) or 3 weeks (in patients with severe disease) • SOC <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Negative conversion of SARS-CoV-2 by Day 28 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • HCQ (n = 75) and SOC (n = 75) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Patients were randomized at a mean of 16.6 days after symptom onset. • 99% of patients had mild or moderate COVID-19. <p>Outcomes:</p> <ul style="list-style-type: none"> • HCQ arm and SOC arm had similar negative PCR conversion rates within 28 days (85.4% of participants vs. 81.3% of participants) and similar times to negative PCR conversion (median of 8 days vs. 7 days). • No difference in the probability of symptom alleviation between the arms in the ITT analysis. 	<p>Limitations:</p> <ul style="list-style-type: none"> • Unclear how the overall rate of symptom alleviation was calculated • Study did not reach target sample size. <p>Interpretation:</p> <ul style="list-style-type: none"> • This study demonstrated no difference in the rate of viral clearance between HCQ and SOC.
High-Dose Chloroquine Versus Low-Dose Chloroquine¹⁵			
<p>Randomized, double-blind, Phase 2b study in hospitalized adults (n = 81)</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged ≥18 years • Clinically suspected COVID-19 • At least 1 of the following conditions: <ul style="list-style-type: none"> • Respiratory rate >24 rpm • Heart rate >125 bpm • SpO₂ <90% on room air • Shock 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • High-dose CQ (n = 41) and low-dose CQ (n = 40) • Planned study sample size was 440 participants, but study was stopped by the study's DSMB. <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • All patients also received ceftriaxone plus AZM. • 89.6% of patients received oseltamivir. 	<p>Limitations:</p> <ul style="list-style-type: none"> • More older patients and more patients with a history of heart disease were randomized into the high-dose arm than into the low-dose arm. <p>Interpretation:</p> <ul style="list-style-type: none"> • Despite the small number of patients enrolled, this study raises concerns about an increased risk of mortality when high-dose CQ is administered in combination with AZM and oseltamivir.

Study Design	Methods	Results	Limitations and Interpretation
High-Dose Chloroquine Versus Low-Dose Chloroquine¹⁵, continued			
	<p>Interventions:</p> <ul style="list-style-type: none"> • CQ 600 mg twice daily for 10 days (high dose) • CQ 450 mg twice daily for 1 day, then CQ 450 mg for 4 days (low dose) <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Mortality by Day 28 	<p>Outcomes:</p> <ul style="list-style-type: none"> • Overall fatality rate was 27.2%. • Mortality by Day 13 was higher in high-dose arm than in low-dose arm (death occurred in 16 of 41 patients [39%] vs. in 6 of 40 patients [15%]; $P = 0.03$). This difference was no longer significant after controlling for age (OR 2.8; 95% CI, 0.9–8.5). • Overall, QTcF >500 ms occurred more frequently in high-dose arm (18.9% of patients) than in low-dose arm (11.1%). • In the high-dose arm, 2 patients experienced ventricular tachycardia before death. 	
Hydroxychloroquine in Nonhospitalized Adults with Early COVID-19¹⁶			
<p>Randomized, placebo-controlled trial in the United States and Canada (n = 491)</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • ≤4 days of symptoms that were compatible with COVID-19 • Either laboratory-confirmed SARS-CoV-2 infection or high-risk exposure within the previous 14 days <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Aged <18 years • Hospitalized • Receipt of certain medications <p>Interventions:</p> <ul style="list-style-type: none"> • HCQ 800 mg once, then HCQ 600 mg in 6 to 8 hours, then HCQ 600 mg once daily for 4 days • Placebo 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • Contributed to primary endpoint data: HCQ (n = 212) and placebo (n = 211) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • 241 patients were exposed to people with COVID-19 through their position as health care workers (57%), 106 were exposed through household contacts (25%), and 76 had other types of exposure (18%). • Median age was 40 years. • 56% of patients were women. • Only 3% of patients were Black. • Very few patients had comorbidities: 11% had hypertension, 4% had diabetes, and 68% had no chronic medical conditions. • 56% of patients were enrolled on Day 1 of symptom onset. • 341 participants (81%) had either a positive PCR result or a high-risk exposure to a PCR-positive contact. 	<p>Limitations:</p> <ul style="list-style-type: none"> • This study enrolled a highly heterogenous population. • Only 227 of 423 participants (53.7%) were confirmed PCR-positive for SARS-CoV-2. • Changing the primary endpoint without a new power calculation makes it difficult to assess whether the study is powered to detect differences in outcomes between the study arms. • This study used surveys for screening, symptom assessment, and adherence reporting. • Visual analog scales are not commonly used, and their ability to assess acute viral respiratory infections in clinical trials has not been validated.

Study Design	Methods	Results	Limitations and Interpretation
Hydroxychloroquine in Nonhospitalized Adults with Early COVID-19¹⁶, continued			
	<p>Primary Endpoints:</p> <ul style="list-style-type: none"> Planned primary endpoint was ordinal outcome by Day 14 in 4 categories: not hospitalized, hospitalized, ICU stay, or death. Because event rates were lower than expected, a new primary endpoint was defined: change in overall symptom severity over 14 days, assessed on a 10-point, self-reported, visual analog scale 	<p>Outcomes:</p> <ul style="list-style-type: none"> Compared to the placebo recipients, HCQ recipients had a nonsignificant 12% difference in improvement in symptoms between baseline and Day 14 (-2.60 vs. -2.33 points; $P = 0.117$). Ongoing symptoms were reported by 24% of those in HCQ arm and 30% of those in the placebo arm at Day 14 ($P = 0.21$). No difference in the incidence of hospitalization (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%; $P < 0.001$). 	<p>Interpretation:</p> <ul style="list-style-type: none"> The study has some limitations, and it did not find evidence that early administration of HCQ reduced symptom severity in patients with mild COVID-19.
Hydroxychloroquine in Nonhospitalized Adults with Mild COVID-19¹⁷			
Open-label RCT in Spain (n = 353)	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> Laboratory-confirmed SARS-CoV-2 infection <5 days of mild COVID-19 symptoms <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> Moderate to severe COVID-19 Severe liver or renal disease History of cardiac arrhythmia QT prolongation <p>Interventions:</p> <ul style="list-style-type: none"> HCQ 800 mg on Day 1, then HCQ 400 mg once daily for 6 days No antiviral treatment 	<p>Number of Participants:</p> <ul style="list-style-type: none"> 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. <p>Participant Characteristics:</p> <ul style="list-style-type: none"> 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. 	<p>Limitations:</p> <ul style="list-style-type: none"> Open-label, non-placebo-controlled trial Study design allowed for the possibility of drop-outs 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. <p>Interpretation:</p> <ul style="list-style-type: none"> 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.

Study Design	Methods	Results	Limitations and Interpretation
Hydroxychloroquine in Nonhospitalized Adults with Mild COVID-19¹⁷, continued			
	<p>Primary Endpoint:</p> <ul style="list-style-type: none"> Reduction in SARS-CoV-2 viral load, assessed using nasopharyngeal swabs on Days 3 and 7 <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> Disease progression up to Day 28 Time to complete resolution of symptoms 	<p>Outcomes:</p> <ul style="list-style-type: none"> No significant difference in viral load reduction between control arm and HCQ arm at Day 3 (-1.41 vs. -1.41 log₁₀ copies/mL; difference of 0.01; 95% CI, -0.28 to 0.29), or at Day 7 (-3.37 vs. -3.44 log₁₀ copies/mL; difference of -0.07; 95% CI, -0.44 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% 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 HCQ arm were not deemed to be related to the drug. 	
Observational Study on Hydroxychloroquine With or Without Azithromycin¹⁸			
<p>Retrospective, multicenter, observational study in a random sample of inpatients with COVID-19 from the New York Department of Health (n = 1,438)</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> Laboratory-confirmed SARS-CoV-2 infection <p>Interventions:</p> <ul style="list-style-type: none"> HCQ plus AZM HCQ alone AZM alone Neither drug <p>Primary Endpoint:</p> <ul style="list-style-type: none"> In-hospital mortality 	<p>Number of Participants:</p> <ul style="list-style-type: none"> HCQ plus AZM (n = 735), HCQ alone (n = 271), AZM alone (n = 211), and neither drug (n = 221) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> Patients in the treatment arms had more severe disease at baseline than those who received neither drug. <p>Outcomes:</p> <ul style="list-style-type: none"> In adjusted analyses, patients who received 1 of the 3 treatment regimens did not show a decreased in-hospital mortality rate when compared with those who received neither drug. 	<p>Limitations:</p> <ul style="list-style-type: none"> This study has the inherent limitations of an observational study, including residual confounding from confounding variables that were unrecognized and/or unavailable for analysis. <p>Interpretation:</p> <ul style="list-style-type: none"> Despite the limitations discussed above, these findings suggest that although HCQ and AZM are not associated with an increased risk of

Study Design	Methods	Results	Limitations and Interpretation
Observational Study on Hydroxychloroquine With or Without Azithromycin¹⁸, continued			
	Secondary Endpoint: <ul style="list-style-type: none"> Cardiac arrest and arrhythmia or QT prolongation on an ECG 	<ul style="list-style-type: none"> Patients who received HCQ plus AZM had a greater risk of cardiac arrest than patients who received neither drug (OR 2.13; 95% CI, 1.12–4.05). 	in-hospital death, the combination of HCQ and AZM may be associated with an increased risk of cardiac arrest.
Observational Study of Hydroxychloroquine Versus No Hydroxychloroquine in New York City¹⁹			
Observational study in hospitalized adults with COVID-19 at a large medical center (n = 1,376)	Key Inclusion Criteria: <ul style="list-style-type: none"> Laboratory-confirmed SARS-CoV-2 infection Key Exclusion Criteria: <ul style="list-style-type: none"> Intubation, death, or transfer to another facility within 24 hours of arriving at the emergency department Interventions: <ul style="list-style-type: none"> HCQ 600 mg twice daily on Day 1, then HCQ 400 mg once daily for 4 days No HCQ Primary Endpoint: <ul style="list-style-type: none"> Time from study baseline (24 hours after patients arrived at the emergency department) to intubation or death 	Number of Participants: <ul style="list-style-type: none"> Received HCQ (n = 811) and did not receive HCQ (n = 565) Participant Characteristics: <ul style="list-style-type: none"> HCQ recipients were more severely ill at baseline than those who did not receive HCQ. Outcomes: <ul style="list-style-type: none"> Using propensity scores to adjust for major predictors of respiratory failure and inverse probability weighting, the study demonstrated that HCQ use was not associated with intubation or death (HR 1.04; 95% CI, 0.82–1.32). No association between concomitant use of AZM and the composite endpoint of intubation or death (HR 1.03; 95% CI, 0.81–1.31). 	Limitations: <ul style="list-style-type: none"> This study has the inherent limitations of an observational study, including residual confounding from confounding variables that were unrecognized and/or unavailable for analysis. Interpretation: <ul style="list-style-type: none"> The use of HCQ for treatment of COVID-19 was not associated with harm or benefit in a large observational study.
Observational Cohort Study of Hydroxychloroquine Versus No Hydroxychloroquine in France²⁰			
Retrospective, observational cohort study in hospitalized adults with severe COVID-19 pneumonia at 4 tertiary care centers (n = 181)	Key Inclusion Criteria: <ul style="list-style-type: none"> Aged 18 to 80 years Laboratory-confirmed SARS-CoV-2 infection Required supplemental oxygen Key Exclusion Criteria: <ul style="list-style-type: none"> Started HCQ before hospital admission 	Number of Participants: <ul style="list-style-type: none"> Received HCQ within 48 hours (n = 84), received HCQ beyond 48 hours (n = 8), and did not receive HCQ (n = 89) Participant Characteristics: <ul style="list-style-type: none"> In the HCQ arm, 18% of patients received concomitant AZM. 	Limitations: <ul style="list-style-type: none"> This was a retrospective, nonrandomized study. Interpretation: <ul style="list-style-type: none"> There was no difference in the rates of clinically important outcomes between patients who received HCQ within 48 hours of hospital admission and those who did not.

Study Design	Methods	Results	Limitations and Interpretation
Observational Cohort Study of Hydroxychloroquine Versus No Hydroxychloroquine in France²⁰ , continued			
	<ul style="list-style-type: none"> • Received tocilizumab, LPV/RTV, or RDV within 48 hours of admission • Organ failure requiring immediate ICU admission • ARDS <p>Interventions:</p> <ul style="list-style-type: none"> • HCQ 600 mg once daily • No HCQ <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Survival without transfer to the ICU at Day 21 <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> • Overall survival rate at Day 21 • Survival rate without ARDS at Day 21 • Weaning from oxygen by Day 21 • Discharge from hospital to home or rehabilitation by Day 21 	<p>Outcomes:</p> <ul style="list-style-type: none"> • In the inverse probability of treatment-weighted analysis, there was no difference in survival rates without ICU transfer at Day 21 between the HCQ arm (76% of participants) and the non-HCQ arm (75%). • No difference between the arms in the secondary outcomes of overall survival rate and survival rate without ARDS at Day 21. 	
Retrospective Cohort Study of Hydroxychloroquine Versus No Hydroxychloroquine in Detroit, Michigan²¹			
Comparative, retrospective cohort study in hospitalized patients with COVID-19 in the Henry Ford Health System in Michigan (n = 2,541)	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Laboratory-confirmed SARS-CoV-2 infection <p>Interventions:</p> <ul style="list-style-type: none"> • HCQ 400 mg twice daily for 1 day, then 200 mg twice daily for 4 days • AZM 500 mg for 1 day, then 250 mg once daily for 4 days • HCQ plus AZM, at the above doses • Neither drug 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • HCQ alone (n = 1,202), AZM alone (n = 147), HCQ plus AZM (n = 783), and neither drug (n = 409) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • HCQ plus AZM was reserved for patients with severe COVID-19 and minimal cardiac risks. • Median patient age was 64 years (IQR 53–76 years); 51% of patients were men, 56% were African American, and 52% had a BMI \geq30. • Median time to follow-up was 28.5 days (IQR 3–53 days). 	<p>Limitations:</p> <ul style="list-style-type: none"> • This study evaluated 1 health care system with an institutional protocol for HCQ and AZM use. • Because the study was not randomized and not blinded, there is a possibility of residual confounding. • There was a lower rate of ICU admission among patients who did not receive HCQ, which suggests that this group may have received less aggressive care.

Study Design	Methods	Results	Limitations and Interpretation
Retrospective Cohort Study of Hydroxychloroquine Versus No Hydroxychloroquine in Detroit, Michigan²¹, continued			
	<p>Primary Endpoint:</p> <ul style="list-style-type: none"> In-hospital mortality 	<ul style="list-style-type: none"> The mSOFA score was not available for 25% of patients. Corticosteroids were given to 79% of patients in the HCQ alone arm, 74% of patients in the HCQ plus AZM arm, and 35.7% of those on neither drug. <p>Outcomes:</p> <ul style="list-style-type: none"> Overall, crude mortality was 18.1%. When broken down by the different arms, mortality was 13.5% in HCQ alone arm, 20.1% in HCQ plus AZM arm, 22.4% in AZM alone arm, and 26.4% in the arm that received neither drug ($P < 0.001$). Mortality HRs were analyzed using a multivariable Cox regression model; the arm that received neither drug was used as the reference. HCQ alone decreased the mortality HR by 66% ($P < 0.001$). HCQ plus AZM decreased the mortality HR by 71% ($P < 0.001$). Other predictors of mortality were age ≥ 65 years (HR 2.6; 95% CI, 1.9–3.3); White race (HR 1.7; 95% CI, 1.4–2.1); chronic kidney disease (HR 1.7; 95% CI, 1.4–2.1); reduced O₂ saturation level on admission (HR 1.6; 95% CI, 1.1–2.2); and ventilator use at admission (HR 2.2; 95% CI, 1.4–3.0). A propensity-matched Cox regression result suggested a mortality HR of 0.487 for patients who received HCQ (95% CI, 0.285–0.832, $P = 0.009$). 	<ul style="list-style-type: none"> Given that the RECOVERY trial showed that dexamethasone use conferred a survival benefit, it is possible that the findings were confounded by the imbalance in corticosteroid use among the arms. <p>Interpretation:</p> <ul style="list-style-type: none"> This study reported a mortality benefit in hospitalized patients with COVID-19 who received either HCQ alone or HCQ plus AZM compared to patients who received neither drug. However, there were substantial imbalances in corticosteroid use among the arms, which may have affected mortality. Because the study was retrospective and observational, it cannot control for confounders.

Key: AE = adverse effect; ARDS = acute respiratory distress syndrome; AV = atrioventricular; AZM = azithromycin; BMI = body mass index; bpm = beats per minute; CQ = chloroquine; DRV/COBI = darunavir/cobicistat; DSMB = data safety monitoring board; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; FiO₂ = fraction of inspired oxygen; GI = gastrointestinal; HCQ = hydroxychloroquine; HFNC = high-flow nasal cannula; ICU = intensive care unit; ITT = intention to treat; LPV/RTV = lopinavir/ritonavir; mSOFA = modified sequential organ failure assessment; the Panel = the COVID-19 Treatment Guidelines Panel; PCR = polymerase chain reaction; QTcF = Fridericia’s correction formula; RCT = randomized controlled trial; RDV = remdesivir; RR = rate ratio; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse effect; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOC = standard of care

References

1. Chorin E, Dai M, Shulman E, et al. The QT interval in patients with COVID-19 treated with hydroxychloroquine and azithromycin. *Nat Med*. 2020;26(6):808-809. Available at: <https://pubmed.ncbi.nlm.nih.gov/32488217>.
2. Gautret P, Lagier JC, Parola P, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study. *Travel Med Infect Dis*. 2020:101663. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32289548>.
3. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32205204>.
4. Huang M, Tang T, Pang P, et al. Treating COVID-19 with chloroquine. *J Mol Cell Biol*. 2020;12(4):322-325. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32236562>.
5. Magagnoli J, Narendran S, Pereira F, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with COVID-19. *Med (N Y)*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32838355>.
6. Molina JM, Delaugerre C, Le Goff J, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. *Med Mal Infect*. 2020;50(4):384. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32240719>.
7. Satlin MJ, Goyal P, Magleby R, et al. Safety, tolerability, and clinical outcomes of hydroxychloroquine for hospitalized patients with coronavirus 2019 disease. *PLoS One*. 2020;15(7):e0236778. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32701969>.
8. Mikami T, Miyashita H, Yamada T, et al. Risk factors for mortality in patients with COVID-19 in New York City. *J Gen Intern Med*. 2020;Published online ahead of print. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32607928>.
9. Catteau L, Dauby N, Montourcy M, et al. Low-dose hydroxychloroquine therapy and mortality in hospitalised patients with COVID-19: a nationwide observational study of 8075 participants. *Int J Antimicrob Agents*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32853673>.
10. COVID-19 RISK and Treatments (CORIST) Collaboration. Use of hydroxychloroquine in hospitalised COVID-19 patients is associated with reduced mortality: findings from the observational multicentre Italian CORIST study. *Eur J Intern Med*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32859477>.
11. Furtado RHM, Berwanger O, Fonseca HA, et al. Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial. *Lancet*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32896292>.
12. Horby P, Mafham M, Linsell L, et al. Effect of hydroxychloroquine in hospitalized patients with COVID-19: preliminary results from a multi-centre, randomized, controlled trial. *medRxiv*. 2020;Preprint. Available at: <https://www.medrxiv.org/content/10.1101/2020.07.15.20151852v1>.
13. Cavalcanti AB, Zampieri FG, Rosa RG, et al. Hydroxychloroquine with or without azithromycin in mild-to-moderate COVID-19. *N Engl J Med*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32706953>.
14. Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. *BMJ*. 2020;369:m1849. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32409561>.

15. Borba MGS, Val FFA, Sampaio VS, et al. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial. *JAMA Netw Open*. 2020;3(4):e208857. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32339248>.
16. Skipper CP, Pastick KA, Engen NW, et al. Hydroxychloroquine in nonhospitalized adults with early COVID-19: a randomized trial. *Ann Intern Med*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32673060>.
17. Mitja O, Corbacho-Monne M, Ubals M, et al. Hydroxychloroquine for early treatment of adults with mild COVID-19: a randomized-controlled trial. *Clin Infect Dis*. 2020;Published online ahead of print. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32674126>.
18. Rosenberg ES, Dufort EM, Udo T, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York state. *JAMA*. 2020;323(24):2493-2502. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32392282>.
19. Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with COVID-19. *N Engl J Med*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32379955>.
20. Mahevas M, Tran VT, Roumier M, et al. Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data. *BMJ*. 2020;369:m1844. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32409486>.
21. Arshad S, Kilgore P, Chaudhry ZS, et al. Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. *Int J Infect Dis*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32623082>.

Ivermectin

Last Updated: February 11, 2021

Ivermectin is a Food and Drug Administration (FDA)-approved antiparasitic drug that is used to treat several neglected tropical diseases, including onchocerciasis, helminthiasis, and scabies.¹ It is also being evaluated for its potential to reduce the rate of malaria transmission by killing mosquitoes that feed on treated humans and livestock.² For these indications, ivermectin has been widely used and is generally well tolerated.^{1,3} Ivermectin is not approved by the FDA for the treatment of any viral infection.

Proposed Mechanism of Action and Rationale for Use in Patients With COVID-19

Reports from in vitro studies suggest that ivermectin acts by inhibiting the host importin alpha/beta-1 nuclear transport proteins, which are part of a key intracellular transport process that viruses hijack to enhance infection by suppressing the host's antiviral response.^{4,5} In addition, ivermectin docking may interfere with the attachment of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein to the human cell membrane.⁶ Ivermectin is thought to be a host-directed agent, which may be the basis for its broad-spectrum activity in vitro against the viruses that cause dengue, Zika, HIV, and yellow fever.^{4,7-9} Despite this in vitro activity, no clinical trials have reported a clinical benefit for ivermectin in patients with these viruses. Some studies of ivermectin have also reported potential anti-inflammatory properties, which have been postulated to be beneficial in people with COVID-19.¹⁰⁻¹²

Some observational cohorts and clinical trials have evaluated the use of ivermectin for the prevention and treatment of COVID-19. Data from some of these studies can be found in [Table 2c](#).

Recommendation

- There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of ivermectin for the treatment of COVID-19. Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of ivermectin in the treatment of COVID-19.

Rationale

Ivermectin has been shown to inhibit the replication of SARS-CoV-2 in cell cultures.¹³ However, pharmacokinetic and pharmacodynamic studies suggest that achieving the plasma concentrations necessary for the antiviral efficacy detected in vitro would require administration of doses up to 100-fold higher than those approved for use in humans.^{14,15} Even though ivermectin appears to accumulate in the lung tissue, predicted systemic plasma and lung tissue concentrations are much lower than 2 μM , the half-maximal inhibitory concentration (IC_{50}) against SARS-CoV-2 in vitro.¹⁶⁻¹⁹ Subcutaneous administration of ivermectin 400 $\mu\text{g}/\text{kg}$ had no effect on SARS-CoV-2 viral loads in hamsters. However, there was a reduction in olfactory deficit (measured using a food-finding test) and a reduction in the interleukin (IL)-6:IL-10 ratio in lung tissues.²⁰

Since the last revision of this section of the Guidelines, the results of several randomized trials and retrospective cohort studies of ivermectin use in patients with COVID-19 have been published in peer-reviewed journals or have been made available as manuscripts ahead of peer review. Some clinical studies showed no benefits or worsening of disease after ivermectin use,²¹⁻²⁴ whereas others reported shorter time to resolution of disease manifestations that were attributed to COVID-19,²⁵⁻²⁸ greater reduction in inflammatory marker levels,^{26,27} shorter time to viral clearance,^{21,26} or lower mortality rates in patients who received ivermectin than in patients who received comparator drugs or placebo.^{21,26,28}

However, most of these studies had incomplete information and significant methodological limitations, which make it difficult to exclude common causes of bias. These limitations include:

- The sample size of most of the trials was small.
- Various doses and schedules of ivermectin were used.
- Some of the randomized controlled trials were open-label studies in which neither the participants nor the investigators were blinded to the treatment arms.
- Patients received various concomitant medications (e.g., doxycycline, hydroxychloroquine, azithromycin, zinc, corticosteroids) in addition to ivermectin or the comparator drug. This confounded the assessment of the efficacy or safety of ivermectin.
- The severity of COVID-19 in the study participants was not always well described.
- The study outcome measures were not always clearly defined.

[Table 2c](#) includes summaries of key studies. Because most of these studies have significant limitations, the Panel cannot draw definitive conclusions on the clinical efficacy of ivermectin for the treatment of COVID-19. Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide further guidance on the role of ivermectin in the treatment of COVID-19.

Monitoring, Adverse Effects, and Drug-Drug Interactions

- Ivermectin is generally well tolerated. Adverse effects may include dizziness, pruritis, nausea, or diarrhea.
- Neurological adverse effects have been reported with the use of ivermectin for the treatment of onchocerciasis and other parasitic diseases, but it is not clear whether these adverse effects were caused by ivermectin or the underlying conditions.²⁹
- Ivermectin is a minor cytochrome P 3A4 substrate and a p-glycoprotein substrate.
- Ivermectin is generally given on an empty stomach with water; however, administering ivermectin with food increases its bioavailability.
- The FDA [issued a warning](#) in April 2020 that ivermectin intended for use in animals **should not be used** to treat COVID-19 in humans.
- Please see [Table 2c](#) for additional information.

Considerations in Pregnancy

In animal studies, ivermectin was shown to be teratogenic when given in doses that were maternotoxic. These results raise concerns about administering ivermectin to people who are in the early stages of pregnancy (prior to 10 weeks gestation).³⁰ A 2020 systematic review and meta-analysis reviewed the incidence of poor maternal and fetal outcomes after ivermectin was used for its antiparasitic properties during pregnancy. However, the study was unable to establish a causal relationship between ivermectin use and poor maternal or fetal outcomes due to the quality of evidence. There are numerous reports of inadvertent ivermectin use in early pregnancy without apparent adverse effects.³¹⁻³³ Therefore, there is insufficient evidence to establish the safety of using ivermectin in pregnant people, especially those in the later stages of pregnancy.

One study reported that the ivermectin concentrations secreted in breastmilk after a single oral dose were relatively low. No studies have evaluated the ivermectin concentrations in breastmilk in patients who received multiple doses.

Considerations in Children

Ivermectin is used in children weighing >15 kg for the treatment of helminthic infections, pediculosis, and scabies. The safety of using ivermectin in children weighing <15 kg has not been well established. Ivermectin is generally well tolerated in children, with a side effect profile similar to the one seen in adults. Currently, there are no available pediatric data from clinical trials to inform the use of ivermectin for the treatment or prevention of COVID-19 in children.

Clinical Trials

Several clinical trials that are evaluating the use of ivermectin for the treatment of COVID-19 are currently underway or in development. Please see [ClinicalTrials.gov](https://www.clinicaltrials.gov) for the latest information.

References

1. Omura S, Crump A. Ivermectin: panacea for resource-poor communities? *Trends Parasitol.* 2014;30(9):445-455. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25130507>.
2. Fritz ML, Siegert PY, Walker ED, Bayoh MN, Vulule JR, Miller JR. Toxicity of bloodmeals from ivermectin-treated cattle to *Anopheles gambiae* s.l. *Ann Trop Med Parasitol.* 2009;103(6):539-547. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19695159>.
3. Kircik LH, Del Rosso JQ, Layton AM, Schaubert J. Over 25 years of clinical experience with ivermectin: an overview of safety for an increasing number of indications. *J Drugs Dermatol.* 2016;15(3):325-332. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26954318>.
4. Yang SNY, Atkinson SC, Wang C, et al. The broad spectrum antiviral ivermectin targets the host nuclear transport importin alpha/beta1 heterodimer. *Antiviral Res.* 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32135219>.
5. Arévalo AP, Pagotto R, Pórfido J, et al. Ivermectin reduces coronavirus infection in vivo: a mouse experimental model. *bioRxiv.* 2020;Preprint. Available at: <https://www.biorxiv.org/content/10.1101/2020.11.02.363242v1>.
6. Lehrer S, Rheinstein PH. Ivermectin docks to the SARS-CoV-2 spike receptor-binding domain attached to ACE2. *In Vivo.* 2020;34(5):3023-3026. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32871846>.
7. Tay MY, Fraser JE, Chan WK, et al. Nuclear localization of dengue virus (DENV) 1-4 non-structural protein 5; protection against all 4 DENV serotypes by the inhibitor ivermectin. *Antiviral Res.* 2013;99(3):301-306. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23769930>.
8. Wagstaff KM, Sivakumaran H, Heaton SM, Harrich D, Jans DA. Ivermectin is a specific inhibitor of importin alpha/beta-mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. *Biochem J.* 2012;443(3):851-856. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22417684>.
9. Barrows NJ, Campos RK, Powell ST, et al. A screen of FDA-approved drugs for inhibitors of Zika virus infection. *Cell Host Microbe.* 2016;20(2):259-270. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27476412>.
10. Zhang X, Song Y, Ci X, et al. Ivermectin inhibits LPS-induced production of inflammatory cytokines and improves LPS-induced survival in mice. *Inflamm Res.* 2008;57(11):524-529. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19109745>.
11. DiNicolantonio JJ, Barroso J, McCarty M. Ivermectin may be a clinically useful anti-inflammatory agent for late-stage COVID-19. *Open Heart.* 2020;7(2). Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32895293>.
12. Ci X, Li H, Yu Q, et al. Avermectin exerts anti-inflammatory effect by downregulating the nuclear transcription factor kappa-B and mitogen-activated protein kinase activation pathway. *Fundam Clin Pharmacol.* 2009;23(4):449-455. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19453757>.
13. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the

- replication of SARS-CoV-2 in vitro. *Antiviral Res.* 2020;178:104787. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32251768>.
14. Chaccour C, Hammann F, Ramon-Garcia S, Rabinovich NR. Ivermectin and COVID-19: keeping rigor in times of urgency. *Am J Trop Med Hyg.* 2020;102(6):1156-1157. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32314704>.
 15. Guzzo CA, Furtek CI, Porras AG, et al. Safety, tolerability, and pharmacokinetics of escalating high doses of ivermectin in healthy adult subjects. *J Clin Pharmacol.* 2002;42(10):1122-1133. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12362927>.
 16. Arshad U, Pertinez H, Box H, et al. Prioritization of anti-SARS-CoV-2 drug repurposing opportunities based on plasma and target site concentrations derived from their established human pharmacokinetics. *Clin Pharmacol Ther.* 2020;108(4):775-790. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32438446>.
 17. Bray M, Rayner C, Noel F, Jans D, Wagstaff K. Ivermectin and COVID-19: a report in antiviral research, widespread interest, an FDA warning, two letters to the editor and the authors' responses. *Antiviral Res.* 2020;178:104805. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32330482>.
 18. Momekov G, Momekova D. Ivermectin as a potential COVID-19 treatment from the pharmacokinetic point of view: antiviral levels are not likely attainable with known dosing regimens. *Biotechnology & Biotechnological Equipment.* 2020;34(1):469-474. Available at: <https://www.tandfonline.com/doi/full/10.1080/13102818.2020.1775118>.
 19. Jermain B, Hanafin PO, Cao Y, Lifschitz A, Lanusse C, Rao GG. Development of a minimal physiologically-based pharmacokinetic model to simulate lung exposure in humans following oral administration of ivermectin for COVID-19 drug repurposing. *J Pharm Sci.* 2020;109(12):3574-3578. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32891630>.
 20. de Melo GD, Lazarini F, Larrous F, et al. Anti-COVID-19 efficacy of ivermectin in the golden hamster. *bioRxiv.* 2020;Preprint. Available at: <https://www.biorxiv.org/content/10.1101/2020.11.21.392639v1>.
 21. Ahmed S, Karim MM, Ross AG, et al. A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. *Int J Infect Dis.* 2020;103:214-216. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33278625>.
 22. Chachar AZK, Khan KA, Asif M, Tanveer K, Khaqan A, Basri R. Effectiveness of ivermectin in SARS-COV-2/COVID-19 Patients. *Int J of Sci.* 2020;9:31-35. Available at: <https://www.ijsciences.com/pub/article/2378>.
 23. Chowdhury ATMM, Shahbaz M, Karim MR, Islam J, Guo D, He S. A randomized trial of ivermectin-doxycycline and hydroxychloroquine-azithromycin therapy on COVID19 patients. *Research Square.* 2020;Preprint. Available at: <https://assets.researchsquare.com/files/rs-38896/v1/3ee350c3-9d3f-4253-85f9-1f17f3af9551.pdf>.
 24. Soto-Becerra P, Culquichicón C, Hurtado-Roca Y, Araujo-Castillo RV. Real-world effectiveness of hydroxychloroquine, azithromycin, and ivermectin among hospitalized COVID-19 patients: results of a target trial emulation using observational data from a nationwide healthcare system in Peru. *medRxiv.* 2020;Preprint. Available at: <https://www.medrxiv.org/content/10.1101/2020.10.06.20208066v3>.
 25. Hashim HA, Maulood MF, Rasheed AW, Fatak DF, Kabah KK, Abdulmir AS. Controlled randomized clinical trial on using ivermectin with doxycycline for treating COVID-19 patients in Baghdad, Iraq. *medRxiv.* 2020;Preprint. Available at: <https://www.medrxiv.org/content/10.1101/2020.10.26.20219345v1/>.
 26. Elgazzar A, Hany B, Youssef SA, Hafez M, Moussa H, Eltaweel A. Efficacy and safety of ivermectin for treatment and prophylaxis of COVID-19 pandemic. *Research Square.* 2020;Preprint. Available at: <https://www.researchsquare.com/article/rs-100956/v2>.
 27. Niaee MS, Gheibi N, Namdar P, et al. Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: a randomized multi-center clinical trial. *Research Square.* 2020;Preprint. Available at: <https://www.researchsquare.com/article/rs-109670/v1>.

28. Khan MSI, Khan MSI, Debnath CR, et al. Ivermectin treatment may improve the prognosis of patients with COVID-19. *Arch Bronconeumol*. 2020;56(12):828-830. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33293006>.
29. Chandler RE. Serious neurological adverse events after ivermectin—do they occur beyond the indication of onchocerciasis? *Am J Trop Med Hyg*. 2018;98(2):382-388. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29210346>.
30. Ivermectin [package insert]. *DailyMed*. 2017. Available at: <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=847a1dd7-d65b-4a0e-a67d-d90392059dac&type=display>.
31. Pacque M, Munoz B, Poetschke G, Foose J, Greene BM, Taylor HR. Pregnancy outcome after inadvertent ivermectin treatment during community-based distribution. *Lancet*. 1990;336(8729):1486-1489. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/1979100>.
32. Chippaux JP, Gardon-Wendel N, Gardon J, Ernould JC. Absence of any adverse effect of inadvertent ivermectin treatment during pregnancy. *Trans R Soc Trop Med Hyg*. 1993;87(3):318. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8236406>.
33. Gyapong JO, Chinbuah MA, Gyapong M. Inadvertent exposure of pregnant women to ivermectin and albendazole during mass drug administration for lymphatic filariasis. *Trop Med Int Health*. 2003;8(12):1093-1101. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14641844>.
34. Ogbuokiri JE, Ozumba BC, Okonkwo PO. Ivermectin levels in human breastmilk. *Eur J Clin Pharmacol*. 1993;45(4):389-390. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8299677>.

Table 2c. Ivermectin: Selected Clinical Data

Last Updated: February 11, 2021

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

Study Design	Methods	Results	Limitations and Interpretation
Ivermectin Versus Ivermectin Plus Doxycycline Versus Placebo for Treatment of COVID-19¹			
Randomized, double-blind, placebo-controlled trial of hospitalized adults in Dhaka, Bangladesh (n = 72)	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged 18–65 years • Laboratory-confirmed SARS-CoV-2 infection with fever, cough, or sore throat • Admitted to hospital within previous 7 days <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Chronic cardiac, renal, or liver disease <p>Interventions:</p> <ul style="list-style-type: none"> • IVM 12 mg PO once daily for 5 days • Single dose of IVM 12 mg PO plus DOX 200 mg PO on Day 1, then DOX 100 mg every 12 hours for 4 days • Placebo <p>Primary Endpoints:</p> <ul style="list-style-type: none"> • Time to virologic clearance, measured by obtaining an NP swab for SARS-CoV-2 PCR on Days 3, 7, and 14, then weekly until PCR result was negative • Resolution of fever and cough within 7 days 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • IVM (n = 24; 2 withdrew), IVM plus DOX (n = 24; 1 withdrew), and placebo (n = 24; 1 withdrew) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Mean age was 42 years. • 54% of participants were female. • Mean time from symptom onset to assessment was 3.83 days. • No patients required supplemental oxygen. <p>Primary Outcomes:</p> <ul style="list-style-type: none"> • Shorter mean time to virologic clearance with IVM than placebo (9.7 days vs. 12.7 days; $P = 0.02$), but not with IVM plus DOX (11.5 days; $P = 0.27$). • Rates of virologic clearance were greater in IVM arm at Day 7 (HR 4.1; 95% CI, 1.1–14.7; $P = 0.03$) and at Day 14 (HR 2.7; 95% CI, 1.2–6.0; $P = 0.02$) compared to placebo, but not in the IVM plus DOX arm (HR 2.3; 95% CI, 0.6–9.0; $P = 0.22$ and HR 1.7; 95% CI, 0.8–4.0; $P = 0.19$). • No statistically significant difference in time to resolution of fever, cough, or sore throat between IVM and placebo arms ($P = 0.35$, $P = 0.18$, and $P = 0.35$, respectively) or IVM plus DOX and placebo arms ($P = 0.09$, $P = 0.23$, and $P = 0.09$, respectively). <p>Other Outcomes:</p> <ul style="list-style-type: none"> • Mean values of CRP, LDH, procalcitonin, and ferritin declined in all arms from baseline to Day 7, but there were no between-arm comparisons of the changes. • No between-arm differences in duration of hospitalization ($P = 0.93$). • No SAEs recorded. 	<p>Limitations:</p> <ul style="list-style-type: none"> • Small sample size • Not clear whether both IVM and DOX placebos were used. • Patients with chronic diseases were excluded. • Disease appears to have been mild in all participants; thus, the reason for hospitalization is unclear. • Absolute changes in inflammatory markers are not presented but were reportedly significant. • PCR results are not a validated surrogate marker for clinical efficacy. <p>Interpretation:</p> <ul style="list-style-type: none"> • A 5-day course of IVM resulted in faster virologic clearance than placebo, but not a faster time to resolution of symptoms (fever, cough, and sore throat). Because time to virologic clearance is not a validated surrogate marker for clinical efficacy, the clinical efficacy of IVM is unknown.

Study Design	Methods	Results	Limitations and Interpretation
Ivermectin Versus Placebo for Outpatients With Mild COVID-19²			
<p>Open-label RCT of adult outpatients in Lahore, Pakistan (n = 50)</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • SARS-CoV-2 PCR positive • Mild disease <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Severe symptoms likely related to cytokine storm • Malignancy, chronic kidney disease, or cirrhosis • Pregnancy <p>Interventions:</p> <ul style="list-style-type: none"> • IVM 12 mg PO immediately, followed by 12 mg doses at 12 and 24 hours, plus symptomatic treatment • Symptomatic treatment <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Symptoms reported on Day 7. Patients were stratified as asymptomatic or symptomatic. 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • IVM (n = 25) and control (n = 25) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Mean age was 40.6 years. • 62% of participants were male. • 40% of participants had diabetes, 30% were smokers, 26% had hypertension, 8% had cardiovascular disease, and 12% had obesity. <p>Outcomes:</p> <ul style="list-style-type: none"> • Proportion of asymptomatic patients at Day 7 was similar in IVM and control arms (64% vs. 60%; <i>P</i> = 0.500). • AEs were attributed to IVM in 8 patients (32%). 	<p>Limitations:</p> <ul style="list-style-type: none"> • Small sample size • Open-label study • Authors reported the proportions of participants with certain symptoms and comorbidities but did not provide objective assessment of disease severity. This precludes the ability to compare outcomes between arms. • Study classified outcomes at Day 7 as “symptomatic” and “asymptomatic,” but did not account for symptom worsening or improvement. <p>Interpretation:</p> <ul style="list-style-type: none"> • IVM showed no effect on symptom resolution in patients with mild COVID-19.
Ivermectin Plus Doxycycline Versus Hydroxychloroquine Plus Azithromycin for Asymptomatic Patients and Patients with Mild to Moderate COVID-19³			
<p>RCT of outpatients with SARS-CoV-2 infection with or without symptoms in Bangladesh (n = 116)</p> <p><i>This is a preliminary report that has not yet been peer reviewed.</i></p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Laboratory-confirmed SARS-CoV-2 infection by RT-PCR • SpO₂ ≥95% • Normal or near-normal CXR • No unstable comorbidities <p>Interventions</p> <p><i>Group A:</i></p> <ul style="list-style-type: none"> • A single dose of IVM 200 µg/kg plus DOX 100 mg twice daily for 10 days 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • Group A (n = 60) and Group B (n = 56) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Mean age was 33.9 years. • 72% of participants were male. • 91 of 116 participants (78.5%) were symptomatic. <p>Outcomes:</p> <ul style="list-style-type: none"> • In Group A, PCR became negative in 60 of 60 patients (100%). Mean time to negative PCR result was 8.93 days (range 8–13 days). 	<p>Limitations:</p> <ul style="list-style-type: none"> • Small sample size • Open-label study • No SOC alone group • Study enrolled young patients without major risk factors for disease progression. • None of the comparative outcome measures were statistically significant.

Study Design	Methods	Results	Limitations and Interpretation
Ivermectin Plus Doxycycline Versus Hydroxychloroquine Plus Azithromycin for Asymptomatic Patients and Patients with Mild to Moderate COVID-19³, continued			
	<p><i>Group B:</i></p> <ul style="list-style-type: none"> • HCQ 400 mg on Day 1, then HCQ 200 mg twice daily for 9 days plus AZM 500 mg once daily for 5 days <p>Primary Endpoints:</p> <ul style="list-style-type: none"> • Time to negative PCR result. Asymptomatic patients were tested starting on Day 5, then every other day until a negative result occurred. Symptomatic patients were tested on their second symptom-free day, then every other day until a negative result occurred. • Time to resolution of symptoms 	<ul style="list-style-type: none"> • In Group B, PCR became negative in 54 of 56 patients (96.4%). Mean time to negative PCR result was 9.33 days (range 5–15 days). • Difference between groups in time from recovery to negative PCR result was not statistically significant ($P = 0.2314$). • In a subgroup analysis of patients who were symptomatic at baseline, the mean durations to negative PCR for Groups A and B were 9.06 days and 9.74 days, respectively ($P = 0.0714$). • In the subgroup analysis, the mean symptom recovery durations for Groups A and B were 5.93 days (range 5–10 days) and 6.99 days (range 4–12 days), respectively ($P = 0.071$). • Patients receiving IVM plus DOX had fewer AEs than those receiving HCQ plus AZM (31.7% vs. 46.4%) in the subgroup analysis. 	<p>Interpretation:</p> <ul style="list-style-type: none"> • In this small study with a young population, the authors suggested that IVM plus DOX was superior to HCQ plus AZM despite no statistically significant difference in time from recovery to negative PCR result and symptom recovery between patients who received IVM plus DOX and those who received HCQ plus AZM.
Effect of Early Treatment With Ivermectin Versus Placebo on Viral Load, Symptoms, and Humoral Response in Patients With Mild COVID-19⁴			
<p>A single-center, randomized, double-blind, placebo-controlled pilot trial in Spain (n = 24)</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Laboratory-confirmed SARS-CoV-2 infection • ≤72 hours of symptoms • No risk factors for severe disease or COVID-19 pneumonia <p>Interventions:</p> <ul style="list-style-type: none"> • Single dose of IVM 400 µg/kg • Nonmatching placebo tablet administered by a nurse who did not participate in the patient's care <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Positive SARS-CoV-2 PCR result from an NP swab at Day 7 post-treatment 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • IVM (n = 12) and placebo (n = 12) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Mean age was 26 years (range 18–54 years). • 50% of participants were male. • All participants had symptoms at baseline; 70% had headache, 66% had fever, 58% had malaise, and 25% had cough. • Median onset of symptoms was 24 hours in IVM arm and 48 hours in placebo arm. <p>Outcomes:</p> <ul style="list-style-type: none"> • At Day 7, 12 patients (100%) in both groups had a positive PCR (for gene N), and 11 of 12 who received IVM (92%) and 12 of 12 who received placebo (100%) had a positive PCR (for gene E); $P = 1.0$ for both comparisons. • In a post hoc analysis, the authors reported fewer patient-days of cough and anosmia in the IVM-treated patients, but no differences in the patient-days for fever, general malaise, headache, and nasal congestion. 	<p>Limitations:</p> <ul style="list-style-type: none"> • Small sample size • PCR is not a validated surrogate marker for clinical efficacy. • PCR cycle threshold values were higher for patients who received IVM than those who received placebo at some time points, but these comparisons are not statistically significant. • Symptom results were not a prespecified outcome and are of unclear statistical and clinical significance. <p>Interpretation:</p> <ul style="list-style-type: none"> • Patients who received IVM showed no difference in viral clearance compared to those who received placebo.

Study Design	Methods	Results	Limitations and Interpretation
Effect of Early Treatment With Ivermectin Versus Placebo on Viral Load, Symptoms, and Humoral Response in Patients With Mild COVID-19⁴, continued			
			<ul style="list-style-type: none"> The small sample size and large number of comparisons make it difficult to assess the clinical efficacy of IVM in this population.
Ivermectin Plus Doxycycline Plus Standard Therapy Versus Standard Therapy Alone in Patients With Mild to Moderate COVID-19⁵			
<p>Randomized, unblinded, single-center study of patients with laboratory-confirmed SARS-CoV-2 infection in Baghdad, Iran (n = 140)</p> <p><i>This is a preliminary report that has not yet been peer reviewed.</i></p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> Diagnosis by clinical, radiological, and PCR testing Outpatients had mild or moderate COVID-19, while inpatients had severe and critical COVID-19. <p>Interventions:</p> <ul style="list-style-type: none"> IVM 200 µg/kg PO daily for 2 days. If patient required more time to recover, a third dose was given 7 days after the first dose, plus DOX 100 mg twice daily for 5–10 days plus standard therapy (based on clinical condition). Standard therapy was based on clinical condition and included AZM, acetaminophen, vitamin C, zinc, vitamin D3, dexamethasone 6 mg daily or methylprednisolone 40 mg twice daily if needed, and oxygen or mechanical ventilation if needed. All critically ill patients were assigned to receive IVM plus DOX. 	<p>Number of Participants:</p> <ul style="list-style-type: none"> IVM plus DOX plus standard therapy (n = 70) and standard therapy alone (n = 70) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> Median age was 50 years in IVM arm and 47 years in standard therapy arm. 50% of patients were male in IVM arm and 53% were male in standard therapy arm. In IVM arm, 48 patients had mild or moderate COVID-19, 11 had severe COVID-19, and 11 had critical COVID-19. In standard therapy arm, 48 patients had mild or moderate COVID-19, 22 had severe COVID-19, and no patients had critical COVID-19. <p>Outcomes:</p> <ul style="list-style-type: none"> Mean recovery time in IVM arm was 10.1 days (SD 5.3 days) vs. 17.9 days (SD 6.8 days) for standard therapy arm ($P < 0.0001$). This result was only significant for those with mild to moderate disease. Disease progression occurred in 3 of 70 patients (4.3%) in IVM arm and 7 of 70 (10.0%) in standard therapy arm ($P = 0.19$) 2 of 70 patients (2.85%) in IVM arm and 6 of 70 (8.57%) in standard therapy arm died ($P = 0.14$) 	<p>Limitations:</p> <ul style="list-style-type: none"> Not blinded Patient deaths prevent an accurate comparison of mean recovery time between arms in this study, and the authors did not account for competing mortality risks. Relies heavily on post hoc subgroup comparisons. Substantial imbalance in disease severity at baseline Authors noted that critical patients were not assigned to standard therapy arm; thus, the arms were not truly randomized. Unclear how many patients required corticosteroids. <p>Interpretation:</p> <ul style="list-style-type: none"> IVM may shorten the time to recovery for patients with mild or moderate disease, but the lack of control for competing mortality causes in the study limits the ability to interpret the results.

Study Design	Methods	Results	Limitations and Interpretation
Efficacy and Safety of Ivermectin Versus Hydroxychloroquine for Treatment of COVID-19⁶			
<p>Multicenter RCT that compared the use of IVM and HCQ in patients with mild, moderate, or severe COVID-19 in hospital settings (n = 400)</p> <p><i>This is a preliminary report that has not yet been peer reviewed.</i></p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Positive RT-PCR result • Mild, moderate, or severe cases of COVID-19 <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Contraindications for HCQ • Critical cases of COVID-19 • Chronic kidney, liver, or heart disease <p>Interventions</p> <p><i>All Patients:</i></p> <ul style="list-style-type: none"> • SOC, which included AZM 500 mg once daily for 6 days, vitamin C 1 gm once daily, zinc 50 mg once daily, lactoferrin 100 mg twice daily, acetylcysteine 200 mg 3 times daily, prophylactic or therapeutic anticoagulation if D-dimer >1,000, and paracetamol as needed. <p><i>Group 1 (Mild or Moderate) and Group 3 (Severe):</i></p> <ul style="list-style-type: none"> • IVM 400 µg/kg once daily for 4 days (maximum of IVM 24 mg per day) <p><i>Group 2 (Mild or Moderate) and Group 4 (Severe):</i></p> <ul style="list-style-type: none"> • HCQ 400 mg every 12 hours on Day 1, then HCQ 200 mg every 12 hours for 5 days <p>Primary Endpoints:</p> <ul style="list-style-type: none"> • Clinical laboratory improvement and/or 2 consecutive negative PCR results ≥48 hours apart • Length of hospital stay 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • All 4 arms (n = 100 in each arm) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Mean age was 53.8–59.6 years. • 67% to 72% of patients were male. • Fatigue and dyspnea reported in 36% to 38% of patients with mild or moderate disease and 86% to 88% of those with severe disease. <p>Primary Outcomes:</p> <ul style="list-style-type: none"> • In those with mild or moderate disease, patients who received IVM had significant differences in improvement compared to those who received HCQ (99% vs. 74%), progression of disease (1% vs. 22%), death (0% vs. 4%), and mean number of hospital days (5±1 vs. 15±8) ($P < 0.001$ for all parameters except death). • For those with severe disease, patients who received IVM had significant differences compared to those who received HCQ in improvement (94% vs. 50%), progression of disease (4% vs. 30%), death (2% vs. 20%), and mean number of hospital days (6±8 vs. 18±8) ($P < 0.001$ for all parameters). • For all patients, those treated with IVM had significant improvement in TLC, CRP, ferritin, D-dimer, and RT-PCR conversion days by Week 1 ($P < 0.001$) compared to those who received HCQ. • In addition to the markers listed above, patients with severe disease showed greater improvement in hemoglobin in IVM arm than in HCQ arm. 	<p>Limitations:</p> <ul style="list-style-type: none"> • Unclear whether the study team and patients were blinded. • The role of SOC therapy in clinical and laboratory responses is unknown. • Cannot rule out potential harm from HCQ. It is unknown whether using AZM plus HCQ could have led to worse outcomes. • No SOC alone group • Laboratory results are only reported after 1 week of treatment. Length of follow up for clinical outcomes and mortality is unclear. <p>Interpretation:</p> <ul style="list-style-type: none"> • Compared to those who received HCQ, IVM recipients had improved inflammatory markers and time to RT-PCR conversion after 1 week. Improvement in clinical status and decreased mortality was also observed in the IVM arm.

Study Design	Methods	Results	Limitations and Interpretation
Antiviral Effect of High-Dose Ivermectin in Adults with COVID-19⁷			
<p>Multicenter, randomized, open-label, blinded trial of hospitalized adults with mild to moderate COVID-19 (n = 45)</p> <p><i>This is a preliminary report that has not yet been peer-reviewed.</i></p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> Laboratory-confirmed SARS-CoV-2 infection Hospitalized with WHO Stage 3 to 5 COVID-19 ≤5 days of symptoms <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> Use of any agent with potential anti-SARS-CoV-2 activity or immunomodulators prior to enrollment Poorly controlled comorbidities <p>Interventions:</p> <ul style="list-style-type: none"> IVM 600 µg/kg once daily plus SOC for 5 days SOC for 5 days <p>Primary Endpoint:</p> <ul style="list-style-type: none"> VL reduction at Day 5. VL was quantified by NP swab at baseline, then at 24, 48, and 72 hours and Day 5. <p>PK Sampling:</p> <ul style="list-style-type: none"> Performed 4 hours after dose on Days 1, 2, 3, 5, and 7 to assess elimination 	<p>Number of Participants:</p> <ul style="list-style-type: none"> IVM (n = 30) and SOC (n = 15) After excluding patients with poor sample quality, those without a detectable VL at baseline, and those who withdrew, 32 patients (20 IVM, 12 SOC) were included in the viral efficacy analysis population. <p>Participant Characteristics:</p> <ul style="list-style-type: none"> Mean age was 40.9 years ± 12.5 years. 56% of patients were male. <p>Primary Outcomes:</p> <ul style="list-style-type: none"> Nonstatistically significant difference in baseline VL between arms. The baseline median VL was 3.74 log₁₀ copies/mL (range 2.8–5.79) in IVM arm and 5.59 log₁₀ copies/mL in SOC arm (P = 0.08). By Day 5, a similar magnitude of viral reduction was seen in both arms. <p>Other Outcomes:</p> <ul style="list-style-type: none"> A significant positive correlation was found after analysis of mean plasma IVM concentration in relation to VL reduction. Participants with higher IVM concentrations had greater reductions in VL (r 0.44; P < 0.04). This correlation was stronger when reduction in VL was related to the IVM exposure corrected by baseline VL (r 0.60; P < 0.004). Treated patients were divided into 2 groups based on IVM C_{max}: IVM >160 ng/mL (median of 202 ng/mL) and ≤160 ng/mL (median of 109 ng/mL). <ul style="list-style-type: none"> Median percentage of VL reduction by C_{max} concentration vs. control (P = 0.0096) was 72% (IQR 59% to 77%) in >160 ng/mL group (n = 9), 40% (IQR 21% to 46%) in ≤160 ng/mL group (n = 11), and 42% (IQR 31% to 73%) in SOC arm. Median viral decay rate (P = 0.041) was 0.64 d⁻¹ in >160 ng/mL group, 0.14 d⁻¹ in ≤160 ng/mL group, and 0.13 d⁻¹ in SOC arm. Percentages of AEs were similar between the arms (43% in IVM arm, 33% in SOC arm), and AEs were mostly mild. No correlation was found between IVM concentration and the occurrence of AEs. 	<p>Limitations:</p> <ul style="list-style-type: none"> Small sample size No clinical response data reported. The C_{max} level of 160 ng/mL used in the analysis appears to be arbitrary. <p>Interpretation:</p> <ul style="list-style-type: none"> Concentration-dependent virologic response was seen using a higher-than-usual dose of IVM (600 µg/kg vs. 200 or 400 µg/kg once daily), with minimal associated toxicities. The study results showed large interpatient variation of IVM C_{max}. Larger sample sizes are needed to further assess the safety and efficacy of using higher doses of IVM to treat COVID-19.

Study Design	Methods	Results	Limitations and Interpretation
Ivermectin as Adjunctive Therapy to Hospitalized Patients With COVID-19⁸			
<p>Randomized, double-blind, placebo-controlled multicenter Phase 2 clinical trial of hospitalized adults with mild to severe SARS-CoV-2 infection in 5 facilities in Iran (n = 180)</p> <p><i>This is a preliminary report that has not yet been peer-reviewed.</i></p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Symptoms suggestive of COVID-19 pneumonia, with chest CT compatible with mild to severe COVID-19 or positive RT-PCR result for SARS-CoV-2 <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Severe immunosuppression, malignancy, or chronic kidney disease • Pregnancy <p>Interventions:</p> <ul style="list-style-type: none"> • HCQ 200 mg/kg twice daily alone as SOC (standard arm) • SOC plus 1 of the following: <ul style="list-style-type: none"> • Placebo • Single dose of IVM 200 µg/kg • IVM 200 µg/kg on Days 1, 3, and 5 • Single dose of IVM 400 µg/kg • IVM 400 µg/kg on Day 1, then IVM 200 µg/kg on Days 3 and 5 <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Clinical recovery within 45 days of enrollment (defined as normal temp, respiratory rate, and SpO₂ >94% for 24 hours) 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • All 6 arms (n = 30 in each arm) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Average age was 56 years (range 45–67 years). • 50% of patients were male. • Disease stratification (based on CT findings): negative (1%), mild (14%), moderate (73%), and severe (12%) • Mean SpO₂ at baseline was 89%. <p>Primary Outcomes:</p> <ul style="list-style-type: none"> • Durations of hypoxemia ($P = 0.025$) and hospitalization ($P = 0.006$) were shorter in the IVM arms compared to placebo arm, and mortality was lower in the IVM arms ($P = 0.001$). • There was no difference in number of days of tachypnea ($P = 0.584$) or return to normal temperature ($P = 0.102$). • Significant differences in change from baseline to Day 5 in absolute lymphocyte count, platelet count, erythrocyte sedimentation rate, and CRP. • Higher mortality was reported in standard and placebo arm than IVM arms. 	<p>Limitations:</p> <ul style="list-style-type: none"> • Small study • Power estimation is confusing. • Mortality was not listed as the primary or secondary outcome. • It is unclear whether IVM patients also received HCQ. • It is unclear whether the between-group comparisons are between combined IVM group and placebo plus SOC. • Participants were stratified by disease severity based on CT findings. These categorizations are unclear and were not taken into account in outcome comparisons. • The post hoc grouping of randomized arms raises risk of false positive findings. <p>Interpretation:</p> <ul style="list-style-type: none"> • IVM appeared to improve laboratory outcomes and some clinical outcomes (shorter duration of hypoxemia and hospitalization) and lowered mortality. • The small size of the study, the unclear treatment arm assignments, and the lack of accounting of disease severity at baseline make it difficult to draw conclusions about the efficacy of using IVM to treat patients with mild COVID-19.

Study Design	Methods	Results	Limitations and Interpretation
Retrospective Analysis of Ivermectin in Hospitalized Patients With COVID-19^a			
<p>Retrospective analysis of consecutive patients with laboratory-confirmed SARS-CoV-2 infection who were admitted to 4 Florida hospitals (n = 276)</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Positive NP swab with SARS-CoV-2 RNA <p>Interventions:</p> <ul style="list-style-type: none"> • Single dose of IVM 200 µg/kg, repeated on Day 7 at the doctors' discretion; 90% percent of patients also received HCQ. • Usual care: 97% of patients received HCQ and most also received AZM. <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • All-cause, in-hospital mortality 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • IVM (n = 173; 160 participants received a single dose, 13 participants received a second dose) and usual care (n = 103) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Mean age was 60.2 years in IVM arm and 58.6 years in the usual care arm. • 51.4% of patients were male in IVM arm and 58.8% were male in usual care arm. • 56.6% of patients were Black in IVM arm and 51.4% were Black in usual care arm. <p>Outcomes:</p> <ul style="list-style-type: none"> • All-cause mortality was lower in IVM arm than in usual care arm (OR 0.27; 95% CI, 0.09–0.80; <i>P</i> = 0.03); the benefit appeared to be limited to the subgroup of patients with severe disease. • No difference in median length of hospital stay between arms (7 days for both) or proportion of mechanically ventilated patients who were successfully extubated (36% in IVM arm vs. 15% in usual care arm; <i>P</i> = 0.07). 	<p>Limitations:</p> <ul style="list-style-type: none"> • Not randomized • Little to no information on oxygen saturation or radiographic findings • Timing of therapeutic interventions was not standardized. • Ventilation and hospitalization duration analyses do not appear to account for death as a competing risk. • No virologic assessments were performed. <p>Interpretation:</p> <ul style="list-style-type: none"> • IVM use was associated with lower mortality than usual care. However, the limitations of this retrospective analysis make it difficult to draw conclusions about the efficacy of using IVM to treat patients with COVID-19.

Study Design	Methods	Results	Limitations and Interpretation
Observational Study on the Effectiveness of Hydroxychloroquine, Azithromycin, and Ivermectin Among Hospitalized Patients With COVID-19¹⁰			
<p>Retrospective cohort study of hospitalized adults with COVID-19 in Peru (n = 5,683)</p> <p><i>This is a preliminary report that has not yet been peer-reviewed.</i></p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged ≥18 years • Symptomatic • Laboratory-confirmed SARS-CoV-2 infection • No life-threatening illness at admission <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Required oxygen at admission • Use of tocilizumab, LPV/RTV, or RDV <p>Interventions:</p> <ul style="list-style-type: none"> • One of the following interventions administered within 48 hours of admission: <ul style="list-style-type: none"> • HCQ or CQ alone • IVM alone • AZM alone • HCQ or CQ plus AZM • IVM plus AZM • SOC (e.g., supportive care, antipyretics, hydration) <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • All-cause mortality <p>Secondary Endpoint:</p> <ul style="list-style-type: none"> • All-cause mortality and/or transfer to ICU 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • HCQ or CQ alone (n = 200), IVM alone (n = 203), AZM alone (n = 1,600), HCQ or CQ plus AZM (n = 692), IVM plus AZM (n = 358), and SOC (n = 2,630) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • 63% of patients were male. • Mean age was 59.4 years (range 18–104 years). • All patients had mild or moderate disease. <p>Outcomes:</p> <ul style="list-style-type: none"> • Median follow-up time was 7 days. Mortality rate was 18.9% at the end of follow up. • IVM alone was associated with increased risk of death and/or ICU transfer compared to SOC (wHR 1.58; 95% CI, 1.11–2.25). • IVM plus AZM did not have an effect on deaths or any secondary outcomes (all-cause death and/or ICU transfer, all-cause death and/or oxygen prescription) compared to SOC. • HCQ or CQ plus AZM was associated with a higher risk of death (wHR 1.84; 95% CI, 1.12–3.02), death and/or ICU transfer (wHR 1.49; 95% CI, 1.01–2.19), and death and/or oxygen prescription (wHR 1.70; 95% CI, 1.07–2.69) compared to SOC. 	<p>Limitations:</p> <ul style="list-style-type: none"> • Not randomized • Unclear whether all patients received IVM or other medications according to Peruvian guidelines referred to in the manuscript. • Dosing and timing of administration are unclear. <p>Interpretation:</p> <ul style="list-style-type: none"> • Compared to SOC, IVM alone was associated with increased risk of death and/or ICU admission. Using IVM in combination with AZM was not associated with effects on mortality, ICU transfer, or oxygen prescription compared to SOC.

Study Design	Methods	Results	Limitations and Interpretation
Retrospective Study of Ivermectin Versus Standard of Care in Patients With COVID-19¹¹			
<p>Retrospective study of consecutive adult patients hospitalized in Bangladesh with laboratory-confirmed SARS-CoV-2 infection (n = 248)</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged ≥18 years • Positive NP swab with SARS-CoV-2 RNA • “Free from any other serious pathological conditions” <p>Interventions:</p> <ul style="list-style-type: none"> • Single dose of IVM 12 mg within 24 hours of hospital admission • SOC <p>Primary Outcome:</p> <ul style="list-style-type: none"> • Not specified 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • IVM (n = 115) and SOC (n = 133) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Median age in IVM arm was 34 years; 70% of participants were male. • Median age in SOC arm was 35 years; 52% of participants were male. • All participants had mild or moderate disease. • 12% of participants had hypertension in both arms. • 17% of participants in IVM arm and 12% in SOC arm had diabetes mellitus. <p>Outcomes:</p> <ul style="list-style-type: none"> • Fewer patients in IVM arm had evidence of disease progression compared to SOC arm ($P < 0.001$): moderate respiratory distress (2.6% vs. 15.8%), pneumonia (0% vs. 9.8%), ischemic stroke (0% vs. 1.5%). • Fewer patients in IVM arm required intensive care management compared to SOC arm (0.9% vs. 8.8%; $P < 0.001$). • Fewer patients in IVM arm required antibiotic therapy (15.7% vs. 60.2%; $P < 0.001$) or supplemental oxygen (9.6% vs. 45.9%; $P < 0.001$) compared to SOC arm. • Shorter median duration of viral clearance in IVM arm compared to SOC arm (4 vs. 15 days; $P < 0.001$). • Shorter median duration of hospital stay in IVM arm compared to SOC arm (9 vs. 15 days; $P < 0.001$) • Lower mortality in IVM arm compared to SOC arm (0.9% vs. 6.8%; $P < 0.05$) 	<p>Limitations:</p> <ul style="list-style-type: none"> • Not randomized • Disease severity at admission was reported as mild or moderate, but 12% of patients in IVM arm and 9% in SOC arm had $SpO_2 < 94\%$ • Even though only 10% of patients developed pneumonia, 60% received antibiotics. • Possibility of harm from concomitant medications <p>Interpretation:</p> <ul style="list-style-type: none"> • Compared to SOC, IVM use was associated with faster rates of viral clearance and better clinical outcomes, including shorter hospital stay and lower mortality

Key: AE = adverse event; AZM = azithromycin; C_{max} = maximum concentration; CQ = chloroquine; CRP = C-reactive protein; CT = computed tomography; CXR = chest X-ray; DOX = doxycycline; HCQ = hydroxychloroquine; ICU = intensive care unit; IVM = ivermectin; LDH = lactose dehydrogenase; LPV/RTV = lopinavir/ritonavir; NP = nasopharyngeal; the Panel = the COVID-19 Treatment Guidelines Panel; PCR = polymerase chain reaction; PK = pharmacokinetic; PO = orally; r = correlation coefficient; RCT = randomized controlled trial; RDV = remdesivir; RT-PCR = reverse transcriptase polymerase chain reaction; SAE = severe adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SD = standard deviation; SOC = standard of care; SpO_2 = oxygen saturation; TLC = total lymphocyte count; VL = viral load; WHO = World Health Organization; wHR = weighted hazard ratio

References

1. Ahmed S, Karim MM, Ross AG, et al. A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. *Int J Infect Dis.* 2020;103:214-216. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33278625>.
2. Chachar AZK, Khan KA, Asif M, Tanveer K, Khaqan A, Basri R. Effectiveness of ivermectin in SARS-COV-2/COVID-19 Patients. *Int J of Sci.* 2020;9:31-35. Available at: <https://www.ijsciences.com/pub/article/2378>.
3. Chowdhury ATMM, Shahbaz M, Karim MR, Islam J, Guo D, He S. A randomized trial of ivermectin-doxycycline and hydroxychloroquine-azithromycin therapy on COVID19 patients. *Research Square.* 2020;Preprint. Available at: <https://assets.researchsquare.com/files/rs-38896/v1/3ee350c3-9d3f-4253-85f9-1f17f3af9551.pdf>.
4. Chaccour C, Casellas A, Blanco-Di Matteo A, et al. The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with non-severe COVID-19: A pilot, double-blind, placebo-controlled, randomized clinical trial. *Lancet.* 2021. Available at: <https://www.thelancet.com/action/showPdf?pii=S2589-5370%2820%2930464-8>.
5. Hashim HA, Maulood MF, Rasheed AW, Fatak DF, Kabah KK, Abdulamir AS. Controlled randomized clinical trial on using ivermectin with doxycycline for treating COVID-19 patients in Baghdad, Iraq. *medRxiv.* 2020;Preprint. Available at: <https://www.medrxiv.org/content/10.1101/2020.10.26.20219345v1/>.
6. Elgazzar A, Hany B, Youssef SA, Hafez M, Moussa H, Eltaweel A. Efficacy and safety of ivermectin for treatment and prophylaxis of COVID-19 pandemic. *Research Square.* 2020;Preprint. Available at: <https://www.researchsquare.com/article/rs-100956/v3>.
7. Krolewiecki A, Lifschitz A, Moragas M, et al. Antiviral effect of high-dose ivermectin in adults with COVID-19: a pilot, randomised, controlled, open label, multicentre trial. *Preprints with the Lancet.* 2020;Preprint. Available at: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3714649.
8. Niaee MS, Gheibi N, Namdar P, et al. Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: a randomized multi-center clinical trial. *Research Square.* 2020;Preprint. Available at: <https://www.researchsquare.com/article/rs-109670/v1>.
9. Rajter JC, Sherman MS, Fatteh N, Vogel F, Sacks J, Rajter JJ. Use of ivermectin is associated with lower mortality in hospitalized patients with coronavirus disease 2019: the ICON study. *Chest.* 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33065103>.
10. Soto-Becerra P, Culquichicón C, Hurtado-Roca Y, Araujo-Castillo RV. Real-world effectiveness of hydroxychloroquine, azithromycin, and ivermectin among hospitalized COVID-19 patients: results of a target trial emulation using observational data from a nationwide healthcare system in Peru. *medRxiv.* 2020;Preprint. Available at: <https://www.medrxiv.org/content/10.1101/2020.10.06.20208066v3>.
11. Khan MSI, Khan MSI, Debnath CR, et al. Ivermectin treatment may improve the prognosis of patients with COVID-19. *Arch Bronconeumol.* 2020;56(12):828-830. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33293006>.

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 [*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.
- 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 [ClinicalTrials.gov](https://clinicaltrials.gov) 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 life-threatening 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 µg/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 (EC₅₀) 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 [archived versions of the Guidelines](#).

References

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: <https://www.ncbi.nlm.nih.gov/pubmed/26868298>.
2. 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: <https://www.ncbi.nlm.nih.gov/pubmed/32641296>.
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>.
4. Group RC. Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33031764>.
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: <https://www.ncbi.nlm.nih.gov/pubmed/32187464>.
7. Chen J, Xia L, Liu L, et al. Antiviral activity and safety of darunavir/cobicistat for the treatment of COVID-19. *Open Forum Infect Dis*. 2020;7(7):ofaa241. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32671131>.
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. *Lancet*. 2020;395(10238):1695-1704. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32401715>.
9. 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: <https://www.sciencedirect.com/science/article/pii/S2666634020300015>.

Table 2d. Characteristics of Antiviral Agents That Are Approved or Under Evaluation for the Treatment of COVID-19

Last Updated: February 11, 2021

- The information in this table is derived from data on the use of these drugs for FDA-approved indications or in investigational trials, and it is supplemented with data on their use in patients with COVID-19, when available.
- There are limited or no data on dose modifications for patients with organ failure or those who require extracorporeal devices. Please refer to product labels, when available.
- There are currently not enough data to determine whether certain medications can be safely coadministered with therapies for the treatment of COVID-19. When using concomitant medications with similar toxicity profiles, consider performing additional safety monitoring.
- The potential additive, antagonistic, or synergistic effects and the safety of using combination therapies for the treatment of COVID-19 are unknown. Clinicians are encouraged to report AEs to the [FDA Medwatch program](#).
- For drug interaction information, please refer to product labels and visit the [Liverpool COVID-19 Drug Interactions website](#).
- For information on drugs that prolong the QTc interval, please visit [CredibleMeds.org](#).

Dosing Regimens <i>The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Chloroquine				
Dose Previously Suggested in an EUA for Adults and Adolescents Weighing ≥50 kg: <ul style="list-style-type: none"> • CQ 1 g PO once on Day 1, then CQ 500 mg PO once daily for 4–7 days of total treatment. Treatment duration should be based on clinical evaluation. 	<ul style="list-style-type: none"> • Prolonged QTc interval, Torsades de Pointes, AV block, ventricular arrhythmia • GI effects (e.g., nausea, vomiting, diarrhea) • Hepatitis • Hypoglycemia • Hemolysis (especially in patients with G6PD deficiency) • Myopathy • Rash 	<ul style="list-style-type: none"> • CBC, hepatic panel, blood glucose, SCr, potassium, magnesium • Baseline ECG • Follow-up ECG if CQ is given with QTc-prolonging drugs or if the patient has underlying cardiac disease 	<ul style="list-style-type: none"> • Additive effect with other drugs that prolong the QTc interval (including AZM) or that cause hypoglycemia • CYP2D6 inhibitor (moderate) • P-gp inhibitor 	<ul style="list-style-type: none"> • The Panel recommends against the use of CQ with or without AZM for the treatment of COVID-19 in hospitalized patients (AI). • In nonhospitalized patients, the Panel recommends against the use of CQ with or without AZM for the treatment of COVID-19, except in a clinical trial (AIa). • The Panel recommends against the use of high-dose CQ (600 mg twice daily for 10 days) for the treatment of COVID-19 (AI). • Dose-dependent toxicity • A list of clinical trials is available here: Chloroquine

Dosing Regimens <i>The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Panel’s Recommendations, Comments, and Links to Clinical Trials
Chloroquine , continued				
	<ul style="list-style-type: none"> Given the risk of heart rhythm problems, the FDA cautions against using CQ to treat COVID-19 outside of a hospital or a clinical trial.¹ 			
Hydroxychloroquine				
<p>Adults:</p> <ul style="list-style-type: none"> Various loading and maintenance doses have been reported in studies or in clinical care. <p>Dose Previously Suggested in an EUA for Hospitalized Adults and Adolescents Weighing ≥50 kg:</p> <ul style="list-style-type: none"> HCQ 800 mg PO once on Day 1, then HCQ 400 mg PO once daily for 4–7 days of total treatment. Treatment duration should be based on clinical evaluation. 	<ul style="list-style-type: none"> Prolonged QTc interval, Torsades de Pointes, AV block, ventricular arrhythmia GI effects (e.g., nausea, vomiting, diarrhea) Hepatitis Hypoglycemia Myopathy Anxiety, agitation, hallucinations, psychosis Allergic reaction/rash Given the risk of heart rhythm problems, the FDA cautions against using HCQ to treat COVID-19 outside of a hospital or a clinical trial.¹ 	<ul style="list-style-type: none"> CBC, hepatic panel, blood glucose, SCr, potassium, magnesium Baseline ECG Follow-up ECG if HCQ is given with QTc-prolonging drugs (e.g., AZM) or if the patient has underlying cardiac disease 	<ul style="list-style-type: none"> Additive effect with other drugs that prolong the QTc interval (including AZM) or that cause hypoglycemia CYP2D6 inhibitor (moderate) P-gp inhibitor 	<ul style="list-style-type: none"> The Panel recommends against the use of HCQ with or without AZM for the treatment of COVID-19 in hospitalized patients (AI). In nonhospitalized patients, the Panel recommends against the use of HCQ with or without AZM for the treatment of COVID-19, except in a clinical trial (Alla). Long elimination; half-life is 40–55 days. Dose-dependent toxicity A list of clinical trials is available here: Hydroxychloroquine

Dosing Regimens <i>The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Ivermectin				
Adults: <ul style="list-style-type: none"> The dose most commonly used in clinical trials is IVM 0.2–0.6 mg/kg given as a single dose or as a once-daily dose for up to 5 days. 	<ul style="list-style-type: none"> Generally well tolerated Dizziness Pruritis GI effects (e.g., nausea, diarrhea) Neurological AEs have been reported with the use of IVM for the treatment of parasitic diseases, but it is not clear whether these AEs were caused by IVM or the underlying conditions. 	<ul style="list-style-type: none"> Monitor for potential AEs. 	<ul style="list-style-type: none"> Minor CYP3A4 substrate P-gp substrate 	<ul style="list-style-type: none"> There are insufficient data for the Panel to recommend either for or against the use of IVM for the treatment of COVID-19. Generally given on an empty stomach with water; however, administering IVM with food increases its bioavailability.² A list of clinical trials is available here: Ivermectin
Lopinavir/Ritonavir				
Adults: <ul style="list-style-type: none"> LPV 400 mg/RTV 100 mg PO twice daily for 10–14 days Neonates Aged ≥14 Days with a PMA ≥42 Weeks and Children Aged <18 Years: <ul style="list-style-type: none"> LPV 300 mg/m² plus RTV 75 mg/m² (maximum dose LPV 400 mg/RTV 100 mg) PO twice daily for a total of 7 days 	<ul style="list-style-type: none"> GI effects (e.g., nausea, vomiting, diarrhea) Transaminase elevation QTc interval prolongation and Torsades de Pointes have been reported. PR interval prolongation 	<ul style="list-style-type: none"> HIV antigen/antibody testing at baseline Serum transaminase levels Consider monitoring ECG when LPV/RTV is given with other QTc-prolonging medications. 	High Drug-Drug Interaction Potential <i>Lopinavir:</i> <ul style="list-style-type: none"> CYP3A4 inhibitor and substrate <i>Ritonavir:</i> <ul style="list-style-type: none"> CYP3A4 > CYP2D6 substrate Potent CYP3A4 and CYP2D6 inhibitor Inducer of UGT1A1 and CYP1A2, CYP2C8, CYP2C9, and CYP2C19 	<ul style="list-style-type: none"> The Panel recommends against the use of LPV/RTV for the treatment of COVID-19 in hospitalized patients (AI). The Panel recommends against the use of LPV/RTV for the treatment of COVID-19 in nonhospitalized patients (AIII). Liquid formulation is commercially available. Crushing LPV/RTV tablets may result in significantly decreased drug exposure (AUC ↓ 45%).³ Use with caution in patients with hepatic impairment. A list of clinical trials is available here: Lopinavir/Ritonavir
Remdesivir				
For Hospitalized Adult and Pediatric Patients (Aged ≥12 Years and Weighing ≥40 kg)	<ul style="list-style-type: none"> Nausea ALT and AST elevations Hypersensitivity 	<ul style="list-style-type: none"> Infusion reactions Renal function, hepatic function, 	<ul style="list-style-type: none"> Clinical drug-drug interaction studies of RDV have not been conducted. 	<ul style="list-style-type: none"> See Therapeutic Management of Patients with COVID-19 for recommendations on using RDV with or without dexamethasone.

Dosing Regimens <i>The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Remdesivir , continued				
<p><i>For Patients Who Are Not Mechanically Ventilated and/or on ECMO:</i></p> <ul style="list-style-type: none"> • RDV 200 mg IV over 30–120 minutes on Day 1, followed by RDV 100 mg IV on Day 2 through Day 5 • In patients who have not shown clinical improvement after 5 days of therapy, treatment may be extended up to 10 days. <p><i>For Mechanically Ventilated Patients and/or Patients on ECMO:</i></p> <ul style="list-style-type: none"> • RDV 200 mg IV over 30–120 minutes on Day 1, followed by RDV 100 mg IV on Day 2 through Day 10 <p>Suggested Dose in EUA^a for Hospitalized Pediatric Patients Weighing 3.5 kg to <40 kg or Aged <12 Years and Weighing ≥3.5 kg</p> <p><i>For Patients Weighing 3.5 kg to <40 kg:</i></p> <ul style="list-style-type: none"> • RDV 5 mg/kg IV over 30–120 minutes on Day 1, followed by RDV 2.5 mg/kg once daily starting on Day 2 • For patients who are not mechanically ventilated and/or on ECMO, the recommended treatment duration is 5 days. If patients have not shown clinical improvement after 5 days of therapy, treatment may be extended up to 10 days. 	<ul style="list-style-type: none"> • Nausea • ALT and AST elevations • Hypersensitivity • Increases in prothrombin time • Drug vehicle is SBECD, which has been associated with renal toxicity. SBECD accumulation may occur in patients with moderate or severe renal impairment. • Each 100 mg vial of RDV lyophilized powder contains 3 g of SBECD and each 100 mg/20 mL vial of RDV solution contains 6 g of SBECD. 	<p>and prothrombin time should be monitored before and during treatment as clinically indicated.</p> <ul style="list-style-type: none"> • Not recommended if eGFR is <30 mL/min • RDV may need to be discontinued if ALT levels increase to >10 times the ULN and should be discontinued if there is an increase in ALT level and signs or symptoms of liver inflammation are observed.⁴ 	<ul style="list-style-type: none"> • In vitro, RDV is a substrate of CYP3A4, OATP1B1, and P-gp and an inhibitor of CYP3A4, OATP1B1, OATP1B3, and MATE1.⁴ • Minimal to no reduction in RDV exposure is expected when RDV is coadministered with dexamethasone (Gilead Sciences, written communication, July 2020). • CQ or HCQ may decrease the antiviral activity of RDV; coadministration of these drugs is not recommended.⁴ • No significant interaction is expected between RDV and oseltamivir or baloxavir (Gilead Sciences, personal and written communications, August and September 2020). 	<ul style="list-style-type: none"> • RDV should be administered in a hospital or a health care setting that can provide a similar level of care to an inpatient hospital. <p>Availability:</p> <ul style="list-style-type: none"> • RDV is approved by the FDA for the treatment of COVID-19 in hospitalized adult and pediatric patients (aged ≥12 years and weighing ≥40 kg). • An EUA^a is available for hospitalized pediatric patients weighing 3.5 kg to <40 kg or aged <12 years and weighing ≥3.5 kg. • A list of clinical trials is available here: Remdesivir

Dosing Regimens <i>The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Remdesivir , continued				
<ul style="list-style-type: none"> For mechanically ventilated patients and/or patients on ECMO, the recommended treatment duration is 10 days. <i>For Patients Aged <12 Years and Weighing ≥40 kg:</i> <ul style="list-style-type: none"> Same dose as for adults and children aged ≥12 years and weighing >40 kg 				

^a The FDA EUA permits the emergency use of RDV for the treatment of suspected COVID-19 or laboratory-confirmed SARS-CoV-2 infection in hospitalized pediatric patients weighing 3.5 kg to <40 kg or aged <12 years and weighing ≥3.5 kg.⁵

Key: AE = adverse event; ALT = alanine transaminase; AST = aspartate aminotransferase; AUC = area under the curve; AV = atrioventricular; AZM = azithromycin; CBC = complete blood count; CQ = chloroquine; CYP = cytochrome P; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; G6PD = glucose-6-phosphate dehydrogenase; GI = gastrointestinal; HCQ = hydroxychloroquine; HIV = human immunodeficiency virus; IV = intravenous; IVM = ivermectin; LPV = lopinavir; LPV/RTV = lopinavir/ritonavir; MATE = multidrug and toxin extrusion protein; OATP = organic anion transporter polypeptide; the Panel = the COVID-19 Treatment Guidelines Panel; P-gp = P-glycoprotein; PMA = postmenstrual age; PO = orally; RDV = remdesivir; RTV = ritonavir; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SBECD = sulfobutylether-beta-cyclodextrin; SCr = serum creatinine; UGT = uridine diphosphate glucuronosyltransferase; ULN = upper limit of normal

References

1. Food and Drug Administration. FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems. 2020. Available at: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or>. Accessed February 3, 2021.
2. Ivermectin (Stromectol) [package insert]. Food and Drug Administration. 2009. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/050742s024s0251bl.pdf.
3. Best BM, Capparelli EV, Diep H, et al. Pharmacokinetics of lopinavir/ritonavir crushed versus whole tablets in children. *J Acquir Immune Defic Syndr*. 2011;58(4):385-391. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21876444>.
4. Remdesivir (Veklury) [package insert]. Food and Drug Administration. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/214787Orig1s0001bl.pdf.
5. Food and Drug Administration. Fact sheet for health care providers emergency use authorization (EUA) of remdesivir (GS-5734™). 2020. Available at: <https://www.fda.gov/media/137566/download>. Accessed February 3, 2021.

Anti-SARS-CoV-2 Antibody Products

Last Updated: February 11, 2021

Summary Recommendations
<ul style="list-style-type: none">• There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of the following products for the treatment of COVID-19:<ul style="list-style-type: none">• COVID-19 convalescent plasma<ul style="list-style-type: none">• The Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the use of convalescent plasma for hospitalized patients with COVID-19 (see Convalescent Plasma for more details).• Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunoglobulins• There are currently insufficient data for the Panel to recommend either for or against the use of the following anti-SARS-CoV-2 monoclonal antibodies for the treatment of nonhospitalized patients with mild to moderate COVID-19:<ul style="list-style-type: none">• Bamlanivimab• The combination of casirivimab plus imdevimab<ul style="list-style-type: none">• The FDA has issued EUAs for the use of bamlanivimab and the casirivimab plus imdevimab combination for nonhospitalized patients with mild to moderate COVID-19 who are at high risk of disease progression (see Anti-SARS-CoV-2 Monoclonal Antibodies for more details).• The FDA also recently issued an EUA for bamlanivimab plus etesevimab for the treatment of certain nonhospitalized patients with mild to moderate COVID-19; the Panel will issue recommendations on the use of this combination shortly.
<p>Rating of Recommendations: A = Strong; B = Moderate; C = Optional</p> <p>Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion</p>

Convalescent Plasma

Last Updated: October 9, 2020

Plasma from donors who have recovered from COVID-19 may contain antibodies to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that may help suppress the virus and modify the inflammatory response.¹

Recommendation

- There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of COVID-19 convalescent plasma for the treatment of COVID-19.

Rationale for Recommendation

Currently, there are insufficient data from well-controlled, adequately powered, randomized clinical trials to evaluate the efficacy and safety of convalescent plasma for the treatment of COVID-19. However, >70,000 patients in the United States have received COVID-19 convalescent plasma through the Mayo Clinic’s Expanded Access Program (EAP), which was designed primarily to provide broad access to investigational convalescent plasma and thus did not include an untreated control arm. Both the Food and Drug Administration (FDA) and the Mayo Clinic performed retrospective, indirect evaluations of efficacy by using the Mayo Clinic EAP data, hypothesizing that patients who received plasma units with higher titers of SARS-CoV-2 neutralizing antibodies would have better clinical outcomes than those who received plasma units with lower antibody titers. The results of their analyses suggest that convalescent plasma with high antibody titers may be more beneficial than low-titer plasma in nonintubated patients, particularly when administered within 72 hours of COVID-19 diagnosis.

The FDA determined that these findings—along with additional data from small randomized and nonrandomized studies, observational cohorts, and animal experiments—met the criteria for Emergency Use Authorization (EUA) issuance.^{2,3} Despite meeting the “may be effective” criterion for EUA issuance, the EAP analyses are not sufficient to establish the efficacy or safety of convalescent plasma due to the lack of a randomized, untreated control group and potential confounding. There is no widely available and generally agreed-upon best test for measuring neutralizing antibodies, and the antibody titers of plasma from patients who have recovered from COVID-19 are highly variable. Furthermore, hospitalized patients with COVID-19 may already have SARS-CoV-2 neutralizing antibody titers that are comparable to those of plasma donors, potentially limiting the benefit of convalescent plasma in this patient population.^{4,5} Several randomized, placebo-controlled trials of COVID-19 convalescent plasma are ongoing.

The Panel’s assessment of the EAP data is consistent with the FDA statements in the convalescent plasma EUA documents.^{3,6,7}

Proposed Mechanism of Action and Rationale for Use in Patients With COVID-19

Adverse Effects

Before administering convalescent plasma to patients with a history of severe allergic or anaphylactic transfusion reactions, the Panel recommends consulting a transfusion medicine specialist who is associated with the hospital blood bank.

The available data suggest that serious adverse reactions following the administration of COVID-19 convalescent plasma are infrequent and consistent with the risks associated with plasma infusions for

other indications. These risks include transfusion-transmitted infections (e.g., human immunodeficiency virus [HIV], hepatitis B, hepatitis C), allergic reactions, anaphylactic reactions, febrile nonhemolytic reactions, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), and hemolytic reactions. Hypothermia, metabolic complications, and post-transfusion purpura have also been described.⁷

Additional risks include a theoretical risk of antibody-dependent enhancement and a theoretical risk of suppressed long-term immunity.

Considerations in Pregnancy

The safety and effectiveness of COVID-19 convalescent plasma during pregnancy have not been evaluated. Several ongoing clinical trials that are evaluating COVID-19 convalescent plasma include pregnant individuals.

Considerations in Children

The safety and effectiveness of COVID-19 convalescent plasma have not been evaluated in pediatric patients. Clinical trials of COVID-19 convalescent plasma in children are ongoing.

Product Availability

On August 23, 2020, the FDA authorized the use of convalescent plasma for the treatment of hospitalized patients with COVID-19.³ Both High Titer (i.e., Ortho VITROS SARS-CoV-2 IgG tested with signal-to-cutoff ratio ≥ 12) and Low Titer COVID-19 Convalescent Plasma are authorized for use.^{6,7} Access to convalescent plasma is no longer available through the Mayo Clinic EAP, which was discontinued on August 28, 2020. Please refer to the [FDA's Recommendations for Investigational COVID-19 Convalescent Plasma website](#) for guidance on the transfusion of investigational convalescent plasma while blood establishments develop the necessary operating procedures to manufacture COVID-19 convalescent plasma in accordance with the Conditions of Authorization set forth in the EUA.

People who have been fully recovered from COVID-19 for ≥ 2 weeks and who are interested in donating plasma can contact their local blood donation or plasma collection center or refer to the FDA's [Donate COVID-19 Plasma](#) website.

Clinical Trials

Randomized clinical trials that are evaluating convalescent plasma for the treatment of COVID-19 are underway; a list is available at [ClinicalTrials.gov](#).

Clinical Data to Date

Open-Label Randomized Clinical Trial of Convalescent Plasma in Hospitalized Patients With Severe or Life-Threatening COVID-19

An open-label randomized clinical trial of convalescent plasma versus standard of care for patients with severe or life-threatening laboratory-confirmed COVID-19 was conducted in Wuhan, China, from February 14 to April 1, 2020. The primary outcome was time to clinical improvement within 28 days. Only plasma units with a SARS-CoV-2 viral spike-receptor binding domain-specific IgG titer of at least 1:640 were transfused. The median time from symptom onset to study randomization was 27 days in the treatment group and 30 days in the control group.⁸

Due to the decreasing incidence of COVID-19 in Wuhan, the trial was terminated early after 103 of the planned 200 patients were enrolled. There was no significant difference between the treatment and control

groups in time to clinical improvement within 28 days (HR 1.40; 95% CI, 0.79–2.49; $P = 0.26$). Among those with severe disease, 91% of the convalescent plasma recipients and 68% of the control patients improved by Day 28 (difference of 23%; OR 1.34; 95% CI, 0.98–1.83; $P = 0.07$). Among those with life-threatening disease, the proportion of patients who showed clinical improvement was similar between the treatment (21%) and control (24%) groups. There was no significant difference in mortality (16% vs. 24% of patients in the treatment and control groups, respectively; $P = 0.30$). At 24 hours, the rates of negative SARS-CoV-2 viral polymerase chain reaction were significantly higher in the convalescent plasma group (45%) than in the control group (15%; $P = 0.003$), and differences persisted at 72 hours.

Limitations

The study was not blinded, and, on average, convalescent plasma was administered approximately 1 month into the disease course. Also, the study was terminated early, and thus lacked sufficient power to detect differences in clinical outcomes between the study groups.

Open-Label Randomized, Multicenter Clinical Trial of Convalescent Plasma in Hospitalized Patients with COVID-19 (ConCOVID Study)

This study has not been peer reviewed.

An open-label randomized clinical trial of convalescent plasma versus standard of care for hospitalized patients with COVID-19 was conducted in 14 hospitals in the Netherlands from April 8 to July 1, 2020. Only plasma confirmed to have anti-SARS-CoV-2 neutralizing antibodies by a SARS-CoV-2 plaque reduction neutralization test (PRNT) and a PRNT50 titer $\geq 1:80$ was transfused. The primary endpoint was in-hospital mortality up to 60 days after admission.

The trial was halted prematurely by the investigators and the study's data safety monitoring board when the baseline SARS-CoV-2 neutralizing antibody titers of participant and convalescent plasma were found to be comparable, challenging the potential benefit of convalescent plasma for the study patient population. Fifty-three of 66 participants had anti-SARS-CoV-2 antibodies at baseline despite being symptomatic for a median time of only 10 days. Among 56 participants whose blood was tested using SARS-CoV-2 plaque reduction neutralization testing, 44 (79%) had neutralizing antibody levels that were comparable to those of 115 donors (median titers of 1:160 vs. 1:160, respectively, $P = 0.40$). When the trial was halted, 86 participants had been enrolled. No differences in mortality ($P = 0.95$), length of hospital stay ($P = 0.68$), or disease severity at Day 15 ($P = 0.58$) were observed between the study arms.⁴

Limitations

The study was terminated early, and thus lacked sufficient power to detect differences in clinical outcomes between the study groups.

Open-Label Randomized, Multicenter Clinical Trial of Convalescent Plasma in Hospitalized Patients with COVID-19 (PLACID Trial)

This study has not been peer reviewed.

An open-label, randomized clinical trial of convalescent plasma versus standard of care for hospitalized patients with COVID-19 was conducted in 39 tertiary care centers in India from April 22 to July 14, 2020. Patients with confirmed COVID-19 and signs of severe disease with hypoxia were eligible if matched donor plasma was available at the time of enrollment. Critically ill patients (those with a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen [$\text{PaO}_2/\text{FiO}_2$] < 200 mmHg or shock) were excluded. The primary outcome was time to disease progression through 28 days (i.e., to $\text{PaO}_2/\text{FiO}_2 < 100$ mmHg) or all-cause mortality at 28 days. Participants in the intervention arm received two doses of 200 mL plasma, transfused 24 hours apart. Antibody testing to assess titers of donated plasma

was not available when the trial started.

Four-hundred and sixty-four participants were randomized; 235 were randomized into the convalescent plasma arm and 229 were randomized into the standard of care arm. The arms were well-balanced with regard to age (median of 52 years in both arms) and days from symptom onset to enrollment (median of 8 days in both arms). There was no difference in the primary outcome (time to disease progression and 28-day mortality) across the trial arms. The composite outcome occurred in 44 patients (18.7%) in the convalescent plasma arm and 41 (17.9%) in the control arm. Thirty-four participants (14.5%) in the convalescent plasma arm and 31 patients in the control arm (13.6%) died. In each arm, 17 participants progressed to severe disease (7.2% in the convalescent plasma arm vs. 7.4% in the standard of care arm).⁵

Limitations

SARS-CoV-2 antibody testing was not used to select donated convalescent plasma units; therefore, many participants may have received units with low titers of SARS-CoV-2 neutralizing antibodies. Additionally, the study was not blinded.

Prospective Safety Analyses and Retrospective Exploratory Analyses of Outcomes Among Tens of Thousands of Patients Receiving Open-Label COVID-19 Convalescent Plasma Through the Mayo Clinic Expanded Access Program

The [Expanded Access to Convalescent Plasma for the Treatment of Patients with COVID-19](#) program was an open-label, nonrandomized EAP that was primarily designed to provide adult patients who have severe or life-threatening (critical) COVID-19 with access to convalescent plasma. Secondary objectives were to obtain data on the safety of the intervention. Exploratory objectives included assessment of 7-day and 28-day mortality. The program was sponsored by the Mayo Clinic and included a diverse range of clinical sites. SARS-CoV-2 antibody testing of plasma donors and assessment of SARS-CoV-2 neutralization potential were not mandated. Patients were transfused with 1 or 2 units (200–500 mL) of convalescent plasma. The main outcomes for the safety analysis were serious adverse events (SAEs), including death; SAEs were reported at 4 hours and at 7 days after transfusion, or as they occurred.^{3,6,9,10}

A peer-reviewed publication described the safety outcomes for the first 20,000 EAP plasma recipients, enrolled between April 3 and June 2, 2020.⁹ One-third of the participants were aged ≥ 70 years, 60% were men, and 71% had severe or life-threatening COVID-19. Twenty percent of the participants were African American, 35% were Hispanic/Latino, and 5% were Asian. Thirteen deaths were assessed as possibly or probably related to the convalescent plasma treatment. The 83 nonfatal SAEs that were assessed as possibly or probably related to the convalescent plasma treatment included 37 TACO events, 20 TRALI events, and 26 severe allergic reactions. The life-threatening events that were reported up to 7 days after transfusion included 87 thrombotic/thromboembolic complications, 406 sustained hypotension events, and 643 cardiac events. The overall mortality rate was 8.6% at 7 days.

Both the FDA and the Mayo Clinic performed retrospective, indirect evaluations of the efficacy of COVID-19 convalescent plasma by using subsets of EAP data, hypothesizing that patients who received plasma units with higher titers of neutralizing antibodies would have better clinical outcomes than those who received plasma units with lower titers of antibodies. This analytic approach was not prespecified in the Mayo Clinic EAP protocol.

The FDA analysis included 4,330 patients, and donor neutralizing antibody titers were measured by the Broad Institute using a pseudovirus assay.⁶ The analysis revealed no difference in 7-day mortality between the patients who received high-titer plasma and those who received low-titer plasma, in the patient population overall, or in the subset of patients who were intubated. However, among nonintubated patients (approximately two-thirds of those analyzed), mortality within 7 days of

transfusion was 11% for those who received high-titer plasma and 14% for those who received low-titer plasma ($P = 0.03$).³ In a post hoc analysis of patients aged <80 years who were not intubated and who were treated within 72 hours of COVID-19 diagnosis, 7-day mortality was lower among the patients who received high-titer plasma than among those who received low-titer plasma (6.3% vs. 11.3%, respectively; $P = 0.0008$).⁶

A similar efficacy analysis by the Mayo Clinic, which has not been peer reviewed, included 3,082 participants who received a single unit of plasma out of the 35,322 participants who had received plasma through the EAP by July 4, 2020. Antibody titers were measured by using the Ortho Clinical Diagnostics COVID-19 IgG assay, and outcomes in patients transfused with low- (lowest 18%), medium-, and high- (highest 17%) titer plasma were compared. After adjusting for baseline characteristics, the 30-day mortality in the low-titer group was 29% and 25% in the high-titer group. This difference did not reach statistical significance. Similar to the FDA analyses, post hoc subgroup analyses suggested a benefit of high-titer plasma in patients aged <80 years who received plasma within 3 days of COVID-19 diagnosis and who were not intubated.¹⁰

Limitations

- The lack of an untreated control arm limits interpretation of the safety and efficacy data. For example, the possibility that differences in outcomes are attributable to harm from low-titer plasma rather than benefit from high-titer plasma cannot be excluded.
- The EAP data may be subject to multiple confounders, including regional differences and temporal trends in the management of COVID-19.
- There is no widely available and generally agreed-upon best test for measuring neutralizing antibodies, and the antibody titers in convalescent plasma from patients who have recovered from COVID-19 are highly variable.
- The efficacy analyses rely on a subset of EAP patients who only represent a fraction of the patients who received convalescent plasma through the EAP.
- The subgroup that demonstrated the largest estimated effect between high-titer and low-titer convalescent plasma—patients aged <80 years who were not intubated and who were transfused within 3 days of COVID-19 diagnosis—was selected post hoc by combining several subset rules which favored subgroups that showed a trend toward benefit of high-titer plasma. This approach tends to overestimate the treatment effect.
- The FDA analysis relied on 7-day mortality, which may not be clinically meaningful in the context of the prolonged disease course of COVID-19. Because participants in this observational study were not rigorously followed after they were discharged from the hospital, the 30-day mortality estimates are uncertain.

Other Clinical Studies of COVID-19 Convalescent Plasma

The results of retrospective case-controlled studies that evaluated outcomes among COVID-19 convalescent plasma recipients have been published.¹¹ In one such study of patients who were hospitalized between March 24 and April 8, 2020, at Mount Sinai Hospital in New York City, outcomes among 39 consecutive patients who received convalescent plasma with a SARS-CoV-2 anti-spike antibody titer of 1:320 were compared to outcomes among 156 propensity-score-matched controls. As of May 1, 2020, 13% of the plasma recipients and 24% of the matched control patients had died ($P = 0.04$, log-rank test), and 72% and 67% of the transfused patients and control patients, respectively, had been discharged from the hospital. Subgroup analyses suggested a benefit of convalescent plasma among patients who were not intubated, had a shorter duration of symptoms, and received therapeutic anticoagulation.

Another study compared convalescent plasma with standard of care in patients with COVID-19 who were hospitalized between March 28 and July 6, 2020, at eight Houston Methodist hospitals. Outcomes for the first 136 convalescent plasma recipients who reached Day 28 post-transfusion were compared with the outcomes for two sets of propensity-score matched controls at 28 days after admission. The analyses suggested a trend towards benefit of convalescent plasma, with larger differences in mortality seen primarily among subgroups of patients who were transfused early (i.e., within 72 hours of admission) with high-titer plasma (i.e., anti-spike protein receptor binding domain titer $\geq 1:1350$).¹²

Other smaller, uncontrolled case series that describe clinical outcomes in patients with COVID-19 have been reported and also suggest that SAEs are uncommon following COVID-19 convalescent plasma treatment.^{1,13-18}

Clinical Data for Other Viral Infections

The use of convalescent plasma has been evaluated for other viral diseases, such as SARS, with some suggestion of potential benefit.¹⁹⁻²¹ The only randomized controlled trial that demonstrated efficacy of convalescent plasma for an infectious disease was conducted more than 40 years ago, for treating Argentine hemorrhagic fever.²² No convalescent plasma products are currently approved by the FDA for the treatment of COVID-19.

References

1. Wang X, Guo X, Xin Q, et al. Neutralizing antibodies responses to SARS-CoV-2 in COVID-19 inpatients and convalescent patients. *Clin Infect Dis*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32497196>.
2. Food and Drug Administration. Convalescent plasma letter of authorization. 2020. Available at: <https://www.fda.gov/media/141477/download>. Accessed August 31, 2020.
3. Food and Drug Administration. EUA 26382: Emergency Use Authorization (EUA) decision memo. 2020 Available at: <https://www.fda.gov/media/141480/download>. Accessed August 31, 2020.
4. Gharbharan A, Jordans CCE, GeurtsvanKessel C, et al. Convalescent plasma for COVID-19: a randomized clinical trial. *medRxiv*. 2020;Preprint. Available at: <https://www.medrxiv.org/content/10.1101/2020.07.01.20139857v1>.
5. Agarwal A, Mukherjee A, Kumar G, et al. Convalescent plasma in the management of moderate COVID-19 in India: an open-label parallel-arm phase II multicentre randomized controlled trial (PLACID Trial). *medRxiv*. 2020;Preprint. Available at: <https://www.medrxiv.org/content/10.1101/2020.09.03.20187252v2>.
6. Food and Drug Administration. EUA 26382: emergency use authorization (EUA) request. 2020. Available at: <https://www.fda.gov/media/141481/download>.
7. Food and Drug Administration. EUA of COVID-19 convalescent plasma for the treatment of COVID-19 in hospitalized patients: fact sheet for health care providers. 2020. Available at: <https://www.fda.gov/media/141478/download>. Accessed September 22, 2020.
8. Li L, Zhang W, Hu Y, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. *JAMA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32492084>.
9. Joyner MJ, Bruno KA, Klassen SA, et al. Safety update: COVID-19 convalescent plasma in 20,000 hospitalized patients. *Mayo Clinical Proceedings*. 2020. Available at: https://mayoclinicproceedings.org/pb/assets/raw/Health%20Advance/journals/jmcp/jmcp_ft95_6_8.pdf. Accessed June 26, 2020.
10. Joyner MJ, Senefeld JW, Klassen SA, et al. Effect of convalescent plasma on mortality among hospitalized patients with COVID-19: initial three-month experience. *medRxiv*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32817978>.
11. Liu STH, Lin HM, Baine I, et al. Convalescent plasma treatment of severe COVID-19: a propensity score-

- matched control study. *Nat Med*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32934372>.
12. Salazar E, Christensen PA, Graviss EA, et al. Treatment of coronavirus disease 2019 patients with convalescent plasma reveals a signal of significantly decreased mortality. *Am J Pathol*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32795424>.
 13. Salazar E, Perez KK, Ashraf M, et al. Treatment of COVID-19 patients with convalescent plasma in Houston, Texas. *medRxiv*. 2020;Preprint. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32511574>.
 14. Ahn JY, Sohn Y, Lee SH, et al. Use of convalescent plasma therapy in two COVID-19 patients with acute respiratory distress syndrome in Korea. *J Korean Med Sci*. 2020;35(14):e149. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32281317>.
 15. Pei S, Yuan X, Zhang Z, et al. Convalescent plasma to treat COVID-19: Chinese strategy and experiences. *medRxiv*. 2020;Preprint. Available at: <https://www.medrxiv.org/content/10.1101/2020.04.07.20056440v1>.
 16. Ye M, Fu D, Ren Y, et al. Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. *J Med Virol*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32293713>.
 17. Zeng Q, Yu Z, Gou J, et al. Effect of convalescent plasma therapy on viral shedding and survival in COVID-19 patients. *The Journal of Infectious Diseases*. 2020;In press. Available at: <https://academic.oup.com/jid/advance-article/doi/10.1093/infdis/jiaa228/5826985>.
 18. Duan K, Liu B, Li C, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. *Proc Natl Acad Sci US*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32253318>.
 19. Burnouf T, Radosевич M. Treatment of severe acute respiratory syndrome with convalescent plasma. *Hong Kong Med J*. 2003;9(4):309; author reply 310. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12904626>.
 20. Cheng Y, Wong R, Soo YO, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. *Eur J Clin Microbiol Infect Dis*. 2005;24(1):44-46. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15616839>.
 21. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. *J Infect Dis*. 2015;211(1):80-90. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25030060>.
 22. Maiztegui JI, Fernandez NJ, de Damián AJ. Efficacy of immune plasma in treatment of Argentine haemorrhagic fever and association between treatment and a late neurological syndrome. *Lancet*. 1979;2(8154):1216-1217. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/92624>.

Immunoglobulins: SARS-CoV-2 Specific

Last Updated: July 17, 2020

Recommendation

- There are insufficient data for the COVID-19 Treatment Guidelines Panel to recommend either for or against **severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunoglobulins** for the treatment of COVID-19.

Rationale

Currently, there are no clinical data on the use of SARS-CoV-2 immunoglobulins. Trials evaluating SARS-CoV-2 immunoglobulins are in development but not yet active and enrolling participants.

Proposed Mechanism of Action and Rationale for Use in Patients with COVID-19

Concentrated antibody preparations derived from pooled plasma collected from individuals who have recovered from COVID-19 can be manufactured as SARS-CoV-2 immunoglobulin, which could potentially suppress the virus and modify the inflammatory response. The use of virus-specific immunoglobulins for other viral infections (e.g., cytomegalovirus [CMV] immunoglobulin for the prevention of post-transplant CMV infection and varicella zoster immunoglobulin for postexposure prophylaxis of varicella in individuals at high-risk) has proven to be safe and effective; however, there are currently no clinical data on the use of such products for COVID-19. Potential risks may include transfusion reactions. Theoretical risks may include antibody-dependent enhancement of infection.

Clinical Data

There are no clinical data on the use of SARS-CoV-2 immunoglobulins for the treatment of COVID-19. Similarly, there are no clinical data on use of specific immunoglobulin or hyperimmunoglobulin products in patients with severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS).

Considerations in Pregnancy

Pathogen-specific immunoglobulins are used clinically during pregnancy to prevent varicella zoster virus (VZV) and rabies and have also been used in clinical trials of therapies for congenital CMV infection.

Considerations in Children

Hyperimmunoglobulin has been used to treat several viral infections in children, including VZV, respiratory syncytial virus, and CMV; efficacy data on their use for other respiratory viruses is limited.

Anti-SARS-CoV-2 Monoclonal Antibodies

Last Updated: February 11, 2021

Bamlanivimab and the combination of casirivimab plus imdevimab are anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) monoclonal antibodies available through Food and Drug Administration (FDA) Emergency Use Authorizations (EUAs) for the treatment of outpatients with mild to moderate COVID-19 who are high risk for progressing to severe disease and/or hospitalization.

Based on the clinical trial data to date (summarized below), the COVID-19 Treatment Guidelines Panel (the Panel) has determined the following:

- There are currently insufficient data to recommend either for or against the use of bamlanivimab or the casirivimab plus imdevimab combination for the treatment of outpatients with mild to moderate COVID-19. The preliminary data on the use of these agents are from Phase 1 and 2 clinical trials that included relatively few participants and reported only a small number of clinical events related to COVID-19. Final results from large Phase 3 randomized controlled trials will further inform the Panel's recommendations on the use of these monoclonal antibodies.
- Health care providers are encouraged to discuss participation in anti-SARS-CoV-2 monoclonal antibody clinical trials, if available, with their patients.
- For high-risk patients who meet EUA criteria for treatment with these monoclonal antibodies, it is appropriate to discuss the potential benefits and risks of the products as part of shared decision making between the patient and the clinician.
- Bamlanivimab and the casirivimab plus imdevimab combination should not be considered standard of care for the treatment of patients with COVID-19.
- There are currently no comparative data to determine whether there are differences in clinical efficacy or safety between bamlanivimab and the casirivimab plus imdevimab combination.
- Patients who are hospitalized because of COVID-19 should not receive bamlanivimab or the casirivimab plus imdevimab combination outside of a clinical trial, although use of the agents can be considered for patients hospitalized for an indication other than COVID-19 who meet EUA use criteria.

Background

The SARS-CoV-2 genome encodes four major structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N) and nonstructural and accessory proteins. The S protein is further divided into two subunits, S1 and S2, that mediate host cell attachment and invasion. Through its receptor-binding domain (RBD), S1 attaches to angiotensin-converting enzyme 2 (ACE2) on the host cell; this initiates a conformational change in S2 resulting in virus-host cell membrane fusion and viral entry.¹

A significant proportion of individuals with COVID-19 produce neutralizing antibodies to SARS-CoV-2 about 10 days after disease onset, with higher antibody levels observed in those with severe disease.² The neutralizing activity of COVID-19 patients' plasma was correlated with the magnitude of antibody responses to SARS-CoV-2 S and N proteins. Monoclonal antibodies targeting the S protein therefore have the potential to prevent SARS-CoV-2 infection and to improve symptomatology and limit progression to severe disease in patients with mild to moderate COVID-19.

Several monoclonal antibodies to SARS-CoV-2 have been developed and characterized.³⁻⁷ Evaluation of their efficacy for the treatment and prevention of COVID-19 is ongoing. In November 2020, the FDA issued two EUAs, one for bamlanivimab and one for the combination of casirivimab plus imdevimab.

The EUAs allow for use of the drugs in nonhospitalized patients (aged ≥ 12 years and weighing ≥ 40 kg) with laboratory confirmed SARS-CoV-2 infection and mild to moderate COVID-19 who are at high risk for progressing to severe disease and/or hospitalization. Administration of the drugs is recommended as soon as possible after a positive SARS-CoV-2 test result and within 10 days of symptom onset. The issuance of an EUA does not constitute FDA approval.

Bamlanivimab (also known as LY-CoV555 and LY3819253) is a neutralizing monoclonal antibody that targets the RBD of the spike protein of SARS-CoV-2. It is administered intravenously as a one-time dose of bamlanivimab 700 mg.

Casirivimab (previously REGN10933) and imdevimab (previously REGN10987) are recombinant human monoclonal antibodies that bind to nonoverlapping epitopes of the spike protein RBD of SARS-CoV-2. The combination of these two antibodies blocks the binding of the RBD to the host cell. The monoclonal antibodies are administered intravenously together as a combined one-time dose of casirivimab 1,200 mg and imdevimab 1,200 mg.

Clinical Trial Data to Date

Bamlanivimab

The Blocking Viral Attachment and Cell Entry with SARS-CoV-2 Neutralizing Antibodies (BLAZE-1) study is a randomized controlled Phase 2 trial comparing three doses of bamlanivimab to placebo.⁸ An interim analysis of this study suggested a potential clinical benefit of bamlanivimab for outpatients with mild to moderate COVID-19 who received the antibody infusion a median of 4 days after symptom onset. In the pooled bamlanivimab arms, five of 309 participants (1.6%) were hospitalized or had emergency department visits versus nine of 143 participants (6.3%) in the placebo arm. In a subset analysis of patients at high risk for hospitalization (using an expanded definition that approximates the bamlanivimab EUA criteria for treatment), four of 136 participants (2.9%) in the pooled bamlanivimab arms versus seven of 69 participants (10.1%) in the placebo arm were hospitalized or had emergency department visits.⁹

Casirivimab Plus Imdevimab

The [R10933-10987-COV-2067](#) study is a randomized controlled Phase 1 and 2 trial comparing two doses of casirivimab plus imdevimab to placebo. An interim analysis of this study suggested a potential clinical benefit of casirivimab plus imdevimab for outpatients with mild to moderate COVID-19 who received an infusion of the drug combination a median of 3 days after symptom onset.¹⁰ In a post hoc analysis submitted to the FDA for the EUA application, eight of 434 participants (2%) in the pooled casirivimab plus imdevimab arms versus 10 of 231 participants (4%) in the placebo arm were hospitalized or had emergency department visits within 28 days of treatment. Among the participants at higher risk for hospitalization (using the EUA definition of high risk and thus approximating the population that would be recommended for treatment), four of 151 participants (3%) in the pooled casirivimab plus imdevimab arms versus seven of 78 participants (9%) in the placebo arm were hospitalized or had emergency department visits.

A published interim analysis of a subset of 275 participants from the [R10933-10987-COV-2067](#) trial suggests that casirivimab plus imdevimab may have a greater effect in participants who test negative for SARS-CoV-2 serum antibodies (endogenous antibodies) at baseline. In this analysis, the proportion of participants who had at least one COVID-19-related medical visit (including hospitalization or emergency department, urgent care, or physician office/telemedicine visit) was lower in the casirivimab plus imdevimab group (6 of 182 participants [3%] for the pooled doses) than in the placebo group (6 of 93 participants [6%]). In the subgroup of participants who were serum antibody negative at baseline, the

intergroup difference in patients with medical visits was greater (5 of 80 participants [6%] in the pooled antibody group and 5 of 33 participants [15%] in the placebo group).¹¹

Please see [Table 3a](#) for additional information.

Based on these study results, the FDA issued EUAs for the use of these monoclonal antibodies in nonhospitalized patients with mild to moderate COVID-19 who are at high risk for progressing to severe disease and/or hospitalization.

The FDA EUAs do not authorize the use of these antibodies for patients who are hospitalized for COVID-19, although their use can be considered for patients who are hospitalized for a non-COVID-19 indication and meet EUA criteria for use of the products. A substudy of A Multicenter, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients With COVID-19 (ACTIV-3) randomized patients hospitalized with COVID-19 to bamlanivimab 7,000 mg or placebo, each in addition to remdesivir. On October 26, 2020, following a prespecified interim futility analysis, enrollment into this study was stopped due to lack of clinical benefit.¹² Among 314 adult hospitalized patients (163 in the bamlanivimab arm and 151 in the placebo arm), pulmonary outcomes were similar at Day 5 (odds ratio of being in a more favorable category in the bamlanivimab arm than in the placebo arm 0.85; 95% CI, 0.56–1.29; $P = 0.45$). The time to hospital discharge was also similar in the two arms (rate ratio 0.97; 95% CI, 0.78–1.20).¹³ Patients who are hospitalized for COVID-19 should not receive bamlanivimab or casirivimab plus imdevimab except in a clinical trial. The FDA EUAs do permit the use of these monoclonal antibodies for patients who are hospitalized for an indication other than COVID-19 provided that they have mild to moderate COVID-19 and are at high risk for progressing to severe disease and/or hospitalization.^{14,15}

Rationale for the Panel's Recommendations

In the studies described above, the number of participants was small, and only a limited number of clinical events (e.g., hospitalizations or emergency department visits) were reported. Given the low number of clinical events, it is difficult to draw definitive conclusions about the efficacy of these anti-SARS-CoV-2 antibodies. In addition, if there is a clinical benefit, there is uncertainty as to which patients are most likely to benefit from these antibodies. Although the published data from the bamlanivimab trial indicate that approximately two-thirds of the patients had a high-risk condition, only 10.7% of those in the antibody arm and 14% of those in the placebo arm were aged ≥ 65 years. In the trial supporting the EUA for casirivimab plus imdevimab (see above), only 34% of the participants were considered high risk. Additional clinical trial data are needed to provide further evidence on the safety and efficacy of these agents and to identify the populations in which the potential benefit will be the greatest.

Please see [Table 3a](#) for additional information.

Monitoring

- Bamlanivimab or casirivimab plus imdevimab should only be administered in health care settings by qualified health care providers who have immediate access to medications to treat severe infusion reactions and to emergency medical services.
- Patients should be monitored during infusion of the agents and then observed for at least 1 hour after the infusion is completed.
- No dosage adjustments are required for body weight, renal impairment, or mild hepatic impairment.

Adverse Effects

- In the BLAZE-1 trial, the most common adverse events of bamlanivimab were nausea, diarrhea, dizziness, headache, pruritis, and vomiting. The safety profile of bamlanivimab at all three doses was reportedly similar to that of the placebo.
- Hypersensitivity, including anaphylaxis and infusion reactions, may occur. According to the EUA for bamlanivimab, among >850 participants in ongoing trials who have received bamlanivimab, one anaphylactic reaction and one serious infusion-related reaction occurred and both required treatment, which in one case included epinephrine.
- According to the EUA fact sheet for casirivimab plus imdevimab, among the 533 participants who received casirivimab plus imdevimab in the R10933-10987-COV-2067 trial, one participant had an anaphylaxis reaction that required treatment with epinephrine, and four participants who received the 8,000 mg dose of the combination (casirivimab 4,000 mg and imdevimab 4,000 mg) had an infusion reaction of grade 2 severity or higher, which, in two cases, resulted in permanent discontinuation of the infusion.

Drug-Drug Interactions

- Drug-drug interactions are unlikely between bamlanivimab or casirivimab plus imdevimab and medications that are renally excreted or that are cytochrome P450 substrates, inhibitors, or inducers.
- Please see [Table 3b](#) for more information.
- For persons who received bamlanivimab or casirivimab plus imdevimab for treatment, vaccination with an mRNA COVID-19 vaccine should be deferred for at least 90 days as a precautionary measure to avoid interference of the antibody treatment with vaccine-induced immune responses.¹⁶

Considerations in Pregnancy

- As immunoglobulin (Ig) G monoclonal antibodies, bamlanivimab and casirivimab plus imdevimab would be expected to cross the placenta. There are no available data on the use of bamlanivimab or casirivimab plus imdevimab during pregnancy; however, IgG products are generally not withheld because of pregnancy when their use is indicated.
- Bamlanivimab and casirivimab plus imdevimab should not be withheld from a pregnant individual with COVID-19 who has a condition that poses a high risk of progression to severe COVID-19, and the patient and provider determine that the potential benefit of the drug outweighs potential risk (see the EUA criteria for the use of bamlanivimab and casirivimab plus imdevimab below).
- Inclusion of pregnant people in clinical trials should be encouraged to inform decisions regarding administration of anti-SARS-CoV-2 antibodies to individuals in this population.

Considerations in Children

- Most children with mild or moderate COVID-19, even those with risk factors specified in the EUAs for bamlanivimab or casirivimab plus imdevimab, will not progress to more severe illness and will recover without specific therapy.
- Risk factors for hospitalization in children with COVID-19 have not been clearly defined to the same extent as in adults, making it difficult to identify those at the highest risk of hospitalization and those who would be likely to benefit from use of bamlanivimab or casirivimab plus imdevimab.
- The use of bamlanivimab or casirivimab plus imdevimab for children who meet the EUA criteria

can be considered on a case-by-case basis in consultation with a pediatric infectious disease specialist. Additional guidance is provided in a recent publication endorsed by the Pediatric Infectious Diseases Society.¹⁷

- Additional data on clinical outcomes in children who receive bamlanivimab or casirivimab plus imdevimab for the treatment of COVID-19, including in those with specific risk factors, are needed.

Clinical Trials

- Several clinical trials that are evaluating bamlanivimab, casirivimab plus imdevimab, and other monoclonal antibodies, alone or in combination, for the treatment of COVID-19 are underway or in development. Please see *ClinicalTrials.gov* for the latest information on [bamlanivimab clinical trials](#) and [casirivimab plus imdevimab clinical trials](#).
- Health care providers are encouraged to discuss participation in anti-SARS-CoV-2 monoclonal antibody clinical trials with patients who have mild to moderate COVID-19.

Drug Availability

- Bamlanivimab and casirivimab plus imdevimab are available through FDA EUAs for outpatients with mild to moderate COVID-19 who are at high risk for progression to severe disease and/or hospitalization.
- Given the possibility of a limited supply of bamlanivimab and casirivimab plus imdevimab, as well as challenges of distributing and administering the drug, patients at highest risk for COVID-19 progression should be prioritized for use through the EUA. In addition, efforts should be made to ensure that communities most affected by COVID-19 have equitable access to bamlanivimab and casirivimab plus imdevimab.

High-Risk Criteria for Emergency Use Authorization of Bamlanivimab or Casirivimab Plus Imdevimab

The FDA EUAs allow for the use of bamlanivimab or casirivimab plus imdevimab for the treatment of mild to moderate COVID-19 in nonhospitalized adults and children aged ≥ 12 years and weighing ≥ 40 kg and who are at high risk for progressing to severe COVID-19 and/or hospitalization. High-risk criteria specified in the EUA are:

- Body mass index (BMI) ≥ 35
- Chronic kidney disease
- Diabetes mellitus
- Immunocompromising condition
- Currently receiving immunosuppressive treatment
- Aged ≥ 65 years
- Aged ≥ 55 years, *and*
 - Cardiovascular disease, *or*
 - Hypertension, *or*
 - Chronic obstructive pulmonary disease or another chronic respiratory disease.
- Aged 12 to 17 years, *and*

- BMI \geq 85th percentile for their age and gender based on [Centers for Disease Control and Prevention growth charts](#), *or*
- Sickle cell disease, *or*
- Congenital or acquired heart disease, *or*
- Neurodevelopmental disorders, for example, cerebral palsy, *or*
- A medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19), *or*
- Asthma, reactive airway, or other chronic respiratory disease that requires daily medication for control.

References

1. Jiang S, Hillyer C, Du L. Neutralizing antibodies against SARS-CoV-2 and other human coronaviruses. *Trends Immunol.* 2020;41(5):355-359. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32249063>.
2. Wang Y, Zhang L, Sang L, et al. Kinetics of viral load and antibody response in relation to COVID-19 severity. *J Clin Invest.* 2020;130(10):5235-5244. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32634129>.
3. Ju B, Zhang Q, Ge J, et al. Human neutralizing antibodies elicited by SARS-CoV-2 infection. *Nature.* 2020;584(7819):115-119. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32454513>.
4. Wang C, Li W, Drabek D, et al. A human monoclonal antibody blocking SARS-CoV-2 infection. *Nat Commun.* 2020;11(1):2251. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32366817>.
5. Cao Y, Su B, Guo X, et al. Potent neutralizing antibodies against SARS-CoV-2 identified by high-throughput single-cell sequencing of convalescent patients' B cells. *Cell.* 2020;182(1):73-84 e16. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32425270>.
6. Zost SJ, Gilchuk P, Chen RE, et al. Rapid isolation and profiling of a diverse panel of human monoclonal antibodies targeting the SARS-CoV-2 spike protein. *Nat Med.* 2020;26(9):1422-1427. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32651581>.
7. Hansen J, Baum A, Pascal KE, et al. Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody cocktail. *Science.* 2020;369(6506):1010-1014. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32540901>.
8. Chen P, Nirula A, Heller B, et al. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with COVID-19. *N Engl J Med.* 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33113295>.
9. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of bamlanivimab. 2020. Available at: <https://www.fda.gov/media/143603/download>. Accessed February 9, 2021.
10. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of casirivimab and imdevimab. 2020. Available at: <https://www.fda.gov/media/143892/download>. Accessed February 9, 2021.
11. Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-COV2, a neutralizing antibody cocktail, in outpatients with COVID-19. *N Engl J Med.* 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33332778>.
12. National Institute of Allergy and Infectious Diseases. Statement—NIH-sponsored ACTIV-3 trial closes LY-CoV555 sub-study. 2020. Available at: <https://www.niaid.nih.gov/news-events/statement-nih-sponsored-activ-3-trial-closes-ly-cov555-sub-study>.
13. ACTIV-3/TICO LY-CoV555 Study Group, Lundgren JD, Grund B, et al. A neutralizing monoclonal antibody for hospitalized patients with COVID-19. *N Engl J Med.* 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33356051>.

14. Food and Drug Administration. Frequently asked questions on the emergency use authorization for bamlanivimab 2020. Available at: <https://www.fda.gov/media/143605/download>. Accessed January 20, 2021.
15. Food and Drug Administration. Frequently asked questions on the emergency use authorization of casirivimab + imdevimab. 2020. Available at: <https://www.fda.gov/media/143894/download>. Accessed January 20, 2021.
16. Centers for Disease Control and Prevention. Interim clinical considerations for use of mRNA COVID-19 vaccines currently authorized in the United States. 2021. Available at: <https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html>. Accessed January 20, 2021.
17. Wolf J, Abzug MJ, Wattier RL, et al. Initial guidance on use of monoclonal antibody therapy for treatment of COVID-19 in children and adolescents. *J Pediatric Infect Dis Soc*. 2021. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33388760>.

Table 3a. Anti-SARS-CoV-2 Monoclonal Antibodies: Selected Clinical Data

Last Updated: February 11, 2021

Study Design	Methods	Results	Limitations and Interpretation
LY-CoV555 (Bamlanivimab) in Outpatients with COVID-19 (BLAZE-1 Interim Analysis)¹			
<p>Double-blind, placebo-controlled, Phase 2 randomized trial in outpatients with mild to moderate COVID-19 (n = 452)</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged ≥ 18 years • Not currently hospitalized • ≥ 1 mild or moderate COVID-19 symptom <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • SpO₂ $\leq 93\%$ on room air, <i>or</i> • Respiratory rate ≥ 30 breaths/min, <i>or</i> • Heart rate ≥ 125 bpm <p>Interventions:</p> <ul style="list-style-type: none"> • Single IV infusion of: <ul style="list-style-type: none"> • BAM 700 mg, <i>or</i> • BAM 2,800 mg, <i>or</i> • BAM 7,000 mg • Placebo • Administered within 3 days after a positive SARS-CoV-2 virologic test result <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Mean decrease in NP SARS-CoV-2 VL from baseline to Day 11 (plus or minus 4 days) <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> • COVID-19-related hospitalization, ED visit, or death within 28 days of treatment • Safety • Symptom burden 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • BAM (n = 309): <ul style="list-style-type: none"> • BAM 700 mg (n = 101) • BAM 2,800 mg (n = 107) • BAM 7,000 mg (n = 101) • Placebo (n = 143) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Median age: 45 years in combined BAM arms (range: 18–86 years) vs. 46 years in placebo arm (range: 18–77 years) • Percentage of participants with risk factors for severe COVID-19: 69.6% in combined BAM arms vs. 66.4% in placebo arm • Percentage of participants aged ≥ 65 years: 10.7% in combined BAM arms vs. 14.0% in placebo arm • Median time from symptom onset to infusion of BAM or placebo: 4 days <p>Primary Outcomes:</p> <ul style="list-style-type: none"> • The mean log change in NP SARS-CoV-2 VL from baseline to Day 11 was significantly greater among participants in the BAM 2,800 mg arm than among those in the placebo arm: -0.53 (95% CI, -0.98 to -0.08; <i>P</i> = 0.02) • The decline in VL was not significantly different between the BAM 700 mg and BAM 7,000 mg arms and the placebo arm. <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> • The number and percentage of participants with COVID-19-related hospitalizations or ED visits within 28 days of treatment was lower among the 	<p>Limitations:</p> <ul style="list-style-type: none"> • Relatively small number of participants in each arm • Low number of hospitalizations or ED visits • NP RT-PCR not a validated surrogate marker of disease progression or recovery • Interim analysis <p>Interpretation:</p> <ul style="list-style-type: none"> • Compared to placebo, a single infusion of BAM 2,800 mg hastened decline of VL at Day 11 among outpatients with mild or moderate COVID-19. This treatment effect was not statistically significant for the other BAM doses. • The clinical meaningfulness of this reduction in VL is unclear. • The combined hospitalization or emergency visit rate was lower in the BAM arms than in the placebo arm, but the number of events in each arm was small. Similar rates were seen for all 3 BAM doses. • Because of the small number of clinical events, it is difficult to draw definitive conclusions about the clinical benefit of BAM; data from larger clinical trials are needed.

Study Design	Methods	Results	Limitations and Interpretation
LY-CoV555 (Bamlanivimab) in Outpatients with COVID-19 (BLAZE-1 Interim Analysis)¹, continued			
		<p>BAM recipients than the placebo recipients:</p> <ul style="list-style-type: none"> • All BAM doses: 5 of 309 (1.6%) • BAM 700 mg: 1 of 101 (1.0%) • BAM 2,800 mg: 2 of 107 (1.9%) • BAM 7,000 mg: 2 of 101 (2.0%) • Placebo: 9 of 143 (6.3%) <ul style="list-style-type: none"> • No deaths reported. • In post hoc analysis of high-risk participants (defined as aged ≥ 65 years or BMI ≥ 35), number and percentage of participants who required hospitalization or ED visit: <ul style="list-style-type: none"> • 4 of 95 (4.2%) in combined BAM arms • 7 of 48 (14.6%) in placebo arm • The change in symptom scores (i.e., improvement from baseline) was slightly better among the BAM recipients than among the placebo recipients. • In the BAM arms, there were no SAEs, and the safety profile of BAM was similar to that of the placebo. 	
LY-CoV555 (Bamlanivimab) in Hospitalized Patients with COVID-19 (ACTIV-3/TICO Preliminary Report)²			
<p>Double-blind, placebo-controlled, randomized trial; a substudy of ACTIV-3/TICO in hospitalized patients with COVID-19 (n = 326)</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Adult hospitalized patients • Documented SARS-CoV-2 infection • Duration of COVID-19 symptoms ≤ 12 days <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • End-organ failure <p>Interventions:</p> <ul style="list-style-type: none"> • Single infusion of BAM 7,000 mg • Placebo 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • mITT analysis (n = 314): BAM 7,000 mg (n = 163) and placebo (n = 151) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Median age: 63 years (range: 50–72 years) in BAM arm vs. 59 years (range: 48–71 years) in placebo arm • Percentage of participants with coexisting illness: 72% in BAM arm vs. 68% in placebo arm • Median days since symptom onset: 7 days (range: 5–9 days) in BAM arm vs. 8 days (range: 5–9 days) in placebo arm 	<p>Limitations:</p> <ul style="list-style-type: none"> • Enrollment was stopped after futility criteria were met, resulting in smaller sample size and limited follow-up period. • Preliminary report <p>Interpretation:</p> <ul style="list-style-type: none"> • No clinical benefit of BAM in hospitalized patients with COVID-19

Study Design	Methods	Results	Limitations and Interpretation
LY-CoV555 (Bamlanivimab) in Hospitalized Patients with COVID-19 (ACTIV-3/TICO Preliminary Report)², continued			
	<ul style="list-style-type: none"> • Participants in both arms received RDV. • All participants received supportive care, which could include supplemental oxygen, and/or glucocorticoids when indicated. <p>Primary Endpoints:</p> <ul style="list-style-type: none"> • Early futility assessments: 2 ordinal outcomes at Day 5 (pulmonary and pulmonary-plus) • Efficacy: Time to a sustained recovery defined as hospital discharge to home and remaining at home for ≥ 14 days • Safety: Composite of death, SAE, or incident grade 3 or 4 AE) <p>Secondary Endpoint:</p> <ul style="list-style-type: none"> • Time to hospital discharge 	<ul style="list-style-type: none"> • Percentage of participants receiving RDV: 37% in BAM arm vs. 44% in placebo arm. • 95% of participants began RDV before or on the day of randomization. • Percentage of participants receiving glucocorticoids: 49% in BAM and placebo arms • Percentage of participants requiring supplemental oxygen: <ul style="list-style-type: none"> • None: 27% in BAM arm vs. 28% in placebo arm • < 4 L/min: 37% in BAM arm vs. 38% in placebo arm • ≥ 4 L/min: 18% in BAM arm vs. 23% in placebo arm • Noninvasive ventilation or high-flow device: 18% in BAM arm vs. 12% in placebo arm • Median duration of follow-up: 31 days <p>Primary Outcomes:</p> <ul style="list-style-type: none"> • The OR of being in a more favorable pulmonary category in the BAM arm than in the placebo arm was 0.85 (95% CI, 0.56–1.29; P = 0.45). • The time to sustained recovery was similar between the arms (rate ratio 1.06; 95% CI, 0.77–1.47). • The percentage of participants with composite safety outcome of death, SAE, or incident grade 3 or 4 AE was 19% in the BAM arm vs. 14% in the placebo arm (OR 1.56; 95% CI, 0.78–3.10). <p>Secondary Outcome:</p> <ul style="list-style-type: none"> • The occurrence of hospital discharge was similar between the 2 arms (rate ratio 0.97; 95% CI, 0.78–1.20). 	<p>Note: The EUA for BAM or CAS plus IMD does not include use in patients hospitalized due to COVID-19.</p>

Study Design	Methods	Results	Limitations and Interpretation
REGN10933 and REGN10987 (Casirivimab Plus Imdevimab) in Outpatients with COVID-19 (R10933-10987-COV-2067)³			
<p>Double-blind, placebo-controlled, Phase 1 and 2 randomized trial in outpatients with mild to moderate COVID-19 (n = 799)</p> <p>Note: These data are from the FDA EUA for CAS plus IMD.</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> Onset of COVID-19 symptoms ≤ 7 days before randomization SpO₂ $\geq 93\%$ on room air <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> Hospitalization before or at randomization due to COVID-19 Prior, current, or planned future use of any of the treatments specified in the protocol (e.g., COVID-19 convalescent plasma, IVIG for any indication) <p>Interventions:</p> <ul style="list-style-type: none"> Single IV infusion of CAS plus IMD combination: <ul style="list-style-type: none"> CAS plus IMD 2,400 mg (CAS 1,200 mg and IMD 1,200 mg), <i>or</i> CAS plus IMD 8,000 mg (CAS 4,000 mg and IMD 4,000 mg) Placebo Administered ≤ 3 days after a positive SARS-CoV-2 virologic test result <p>Primary Endpoint:</p> <ul style="list-style-type: none"> TWA change in NP VL from baseline to Day 7 <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> COVID-19-related medical visits including hospitalization or ED, urgent care, or physician office/telemedicine visits within 28 days of treatment Safety Symptom improvement 	<p>Number of Participants:</p> <ul style="list-style-type: none"> CAS plus IMD (n = 533): <ul style="list-style-type: none"> CAS plus IMD 2,400 mg (n = 266) CAS plus IMD 8,000 mg (n = 267) Placebo (n = 266) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> Median age: 42 years (7% aged ≥ 65 years) Percentage of participants with risk factors for severe COVID-19: 34% Median duration of symptoms: 3 days <p>Primary Outcomes:</p> <ul style="list-style-type: none"> Evaluated in the modified full analysis set of participants with detectable virus at baseline (n = 665) TWA change in NP VL at Day 7 was greater among the CAS plus IMD-treated participants overall than among the placebo-treated participants (-0.36 log₁₀ copies/mL; $P < 0.0001$). <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> The proportion of participants who had COVID-19-related medical visits within 28 days of treatment was lower in the combined CAS plus IMD arms than in the placebo arm: <ul style="list-style-type: none"> Combined CAS plus IMD arms: 2.8% of patients Placebo arm: 6.5% of patients In a post hoc analysis, the number and percentage of participants who were hospitalized or had a medical visit within 28 days of treatment: <ul style="list-style-type: none"> All CAS plus IMD doses: 8 of 434 (2%) CAS plus IMD 2,400 mg: 4 of 215 (2%) CAS plus IMD 8,000 mg: 4 of 219 (2%) Placebo: 10 of 231 (4%) 	<p>Limitations:</p> <ul style="list-style-type: none"> Relatively small number of participants in each arm Low number of hospitalizations or ED visits NP RT-PCR is not a validated surrogate marker of disease progression or recovery. <p>Interpretation:</p> <ul style="list-style-type: none"> Compared to placebo, a single infusion of CAS plus IMD showed a reduction in VL at Day 7 among outpatients with mild or moderate COVID-19. The clinical meaningfulness of this reduction in VL is unclear. Combined hospitalization or ED visit rate was lower in CAS plus IMD arms than in the placebo arm, but the number of events in each arm was small. Because of the small number of clinical events, it is difficult to draw definitive conclusions about the clinical benefit of CAS plus IMD; more information is needed.

Study Design	Methods	Results	Limitations and Interpretation
REGN10933 and REGN10987 (Casirivimab Plus Imdevimab) in Outpatients with COVID-19 (R10933-10987-COV-2067)³, continued			
		<ul style="list-style-type: none"> • In a post hoc analysis, the number and percentage of participants at high-risk for progression to severe COVID-19 and/or hospitalization who required hospitalization or ED visit: <ul style="list-style-type: none"> • All CAS plus IMD doses: 4 of 151 (3%) • Placebo: 7 of 78 (9%) • Median time to symptom improvement: <ul style="list-style-type: none"> • Combined CAS plus IMD arms: 5 days • Placebo arm: 6 days • The safety profile of CAS plus IMD was similar to that of placebo. • 4 infusion related reactions of grade 2 severity or higher were reported in the CAS plus IMD 8,000 mg arm resulting in permanent discontinuation of the infusion in 2 participants; 1 participant had an anaphylactic reaction that resolved with treatment. 	
Published Preliminary Subset Analysis of REGN10933 (Casirivimab) Plus REGN10987 (Imdevimab) in Outpatients with COVID-19 (R10933-10987-COV-2067 Interim Analysis)⁴			
Note: The data presented in this interim analysis represent a subset of participants described in the EUA above.			
<p>Double-blind, placebo-controlled, Phase 1 and 2 randomized trial in outpatients with mild to moderate COVID-19 (n = 275)</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Onset of COVID-19 symptoms <7 days • SpO₂ ≥93% on room air <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Hospitalization before or at randomization due to COVID-19 • Prior, current, or planned future use of any of the treatments specified in the protocol (e.g., COVID-19 convalescent plasma, IVIG for any indication) 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • All CAS plus IMD doses (n = 182): <ul style="list-style-type: none"> • CAS plus IMD 2,400 mg (n = 92) • CAS plus IMD 8,000 mg (n = 90) • Placebo (n = 93) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Median age: 44 years (range: 35–52 years) • Median time from symptom onset to randomization: 3 days • Baseline serum antibody status: <ul style="list-style-type: none"> • Positive: 45% of participants • Negative: 41% of participants 	<p>Limitations:</p> <ul style="list-style-type: none"> • No formal hypothesis testing • Interim analysis • Relatively small number of participants in each arm • These data represent only a subset of participants described in the EUA (above). • Low number of medical visits • NP RT-PCR is not a validated surrogate marker of disease progression or recovery.

Study Design	Methods	Results	Limitations and Interpretation
Published Preliminary Subset Analysis of REGN10933 (Casirivimab) Plus REGN10987 (Imdevimab) in Outpatients with COVID-19 (R10933-10987-COV-2067 Interim Analysis)⁴, continued			
	<p>Interventions:</p> <ul style="list-style-type: none"> • Single IV infusion of CAS plus IMD combination: <ul style="list-style-type: none"> • CAS plus IMD 2,400 mg (CAS 1,200 mg and IMD 1,200 mg) or • CAS plus IMD 8,000 mg (CAS 4,000 mg and IMD 4,000 mg) • Placebo • Administered ≤3 days after a positive SARS-CoV-2 virologic test result <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • TWA change in NP VL from baseline to Day 7 in participants with negative serum antibody status at baseline <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> • COVID-19-related medical visits, including hospitalization or ED, urgent care, or physician office/telemedicine visits within 28 days of treatment • Safety • Symptom improvement 	<ul style="list-style-type: none"> • Unknown: 14% of participants <p>Primary Outcomes:</p> <ul style="list-style-type: none"> • Evaluated in modified full analysis set of participants with detectable virus at baseline (n = 221) • TWA change in NP VL at Day 7 was greater among the participants who received CAS plus IMD ($-1.74 \pm 0.11 \log_{10}$ copies/mL; CI, -1.95 to -1.53) than among those who received placebo ($-1.34 \pm 0.13 \log_{10}$ copies/mL; CI, -1.60 to -1.08). • Among the participants with a negative serum antibody status at baseline, TWA change in VL was greater among those who received CAS plus IMD ($-1.94 \pm 0.13 \log_{10}$ copies/mL; CI: -2.20 to -1.67) than among those who received placebo ($-1.37 \pm 0.20 \log_{10}$ copies/mL; CI, -1.76 to -0.98). <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> • Compared to the placebo participants, the CAS plus IMD participants had fewer COVID-19-related medical visits within 28 days of treatment: <ul style="list-style-type: none"> • All CAS plus IMD doses: 6 of 182 (3%) • Placebo: 6 of 93 (6%) • Among participants with negative serum antibody status at baseline, those who received CAS plus IMD had fewer COVID-19-related medical visits within 28 days of treatment: <ul style="list-style-type: none"> • All CAS plus IMD doses: 5 of 80 (6%) • Placebo: 5 of 33 (15%) • The safety profile of CAS plus IMD was similar to that of the placebo; 2 hypersensitivity or infusion related reactions of grade 2 severity or higher were reported in both the CAS plus IMD 8,000 mg arm and the placebo arm. • The mean half-life for both CAS and IMD antibodies ranged from 25–37 days. 	<p>Interpretation:</p> <ul style="list-style-type: none"> • Compared to placebo, a single infusion of CAS plus IMD showed a reduction in VL at Day 7 among outpatients with mild or moderate COVID-19. • The clinical meaningfulness of this reduction in VL is unclear. • The percentage of participants with medical visits was lower in the CAS plus IMD arms than in the placebo arm, but the number of events in each arm was small. • CAS plus IMD may have a greater effect in patients with a negative serum antibody status but further investigation is needed. • Because of the small number of clinical events, it is difficult to draw definitive conclusions about the clinical benefit of CAS plus IMD; more information is needed.

Key: AE = adverse event; BAM = bamlanivimab; BMI = body mass index; CAS = casirivimab; EUA = Emergency Use Authorization; ED = emergency department; IMD = imdevimab; IV = intravenous; IVIG = intravenous immunoglobulin; mITT = modified intention to treat; NP = nasopharyngeal; RDV = remdesivir; RT-PCR = reverse transcriptase-polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SpO₂ = saturation of oxygen; TWA = time-weighted average; VL = viral load

References

1. Chen P, Nirula A, Heller B, et al. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with COVID-19. *N Engl J Med*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33113295>.
2. Activ-Tico Ly- CoV555 Study Group, Lundgren JD, Grund B, et al. A neutralizing monoclonal antibody for hospitalized patients with COVID-19. *N Engl J Med*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33356051>.
3. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of casirivimab and imdevimab. 2020. Available at: <https://www.fda.gov/media/143892/download>. Accessed November 13, 2020.
4. Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-COV2, a neutralizing antibody cocktail, in outpatients with COVID-19. *N Engl J Med*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33332778>.

Table 3b. Characteristics of SARS-CoV-2 Antibody-Based Products Under Evaluation for the Treatment of COVID-19

Last Updated: February 11, 2021

- The information in this table is derived from data on the use of these products in investigational trials in patients with COVID-19. The table includes dose recommendations from the FDA EUAs for patients with COVID-19 who meet specified criteria.
- There are limited or no data on dose modifications for patients with organ failure or those who require extracorporeal devices. Please refer to product labels, when available.
- There are currently not enough data to determine whether certain medications can be safely coadministered with therapies for the treatment of COVID-19. When using concomitant medications with similar toxicity profiles, consider performing additional safety monitoring.
- The potential additive, antagonistic, or synergistic effects and the safety of using combination therapies for the treatment of COVID-19 are unknown. Clinicians are encouraged to report AEs to the [FDA Medwatch program](#).

Dosing Regimens	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Bamlanivimab (Anti-SARS-CoV-2 Monoclonal Antibody)				
<p>Dose Recommended in an EUA for Nonhospitalized Adult and Pediatric Patients (Aged ≥12 Years and Weighing ≥40 kg) With Mild to Moderate COVID-19 Who are at High Risk for Progressing to Severe COVID-19 and/or Hospitalization:</p> <ul style="list-style-type: none"> • Single dose of BAM 700 mg IV as soon as possible after a positive result on viral test for SARS-CoV-2 and within 10 days of symptom onset (per EUA) 	<ul style="list-style-type: none"> • Nausea • Diarrhea • Dizziness • Headache • Pruritis • Vomiting • Hypersensitivity, including anaphylaxis and infusion reactions • Unexpected SAEs may occur. 	<ul style="list-style-type: none"> • Only for administration in health care settings by qualified health care providers who have immediate access to medications to treat a severe infusion reaction and emergency medical services. • Monitor patient during the infusion and then observe for ≥1 hour after the infusion is completed. 	<ul style="list-style-type: none"> • Drug-drug interactions are unlikely between BAM and medications that are renally excreted or that are CYP substrates, inhibitors, or inducers. 	<ul style="list-style-type: none"> • To date, there are insufficient data for the Panel to recommend either for or against the use of BAM for the treatment of outpatients with mild to moderate COVID-19. • Patients who are hospitalized for COVID-19 should not receive BAM outside of a clinical trial. • A list of clinical trials is available: Bamlanivimab <p>Availability:</p> <ul style="list-style-type: none"> • BAM is available through the FDA EUA for high-risk outpatients with mild to moderate COVID-19.¹ See Anti-SARS-CoV-2 Monoclonal Antibodies for a list of high-risk conditions.

Dosing Regimens	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Casirivimab Plus Imdevimab (Anti-SARS-CoV-2 Monoclonal Antibodies)				
<p>Dose Recommended in an EUA For Nonhospitalized Adult and Pediatric Patients (Aged ≥12 Years and Weighing ≥40 kg) With Mild to Moderate COVID-19 Who are at High Risk for Progressing to Severe COVID-19 and/or Hospitalization:</p> <ul style="list-style-type: none"> CAS 1,200 mg and IMD 1,200 mg IV administered together once in a single dose as soon as possible after positive result on viral test for SARS-CoV-2 and within 10 days of symptom onset (per EUA) 	<ul style="list-style-type: none"> Hypersensitivity, including anaphylaxis and infusion reactions Unexpected SAEs may occur. 	<ul style="list-style-type: none"> Only for administration in health care settings by qualified health care providers who have immediate access to medications to treat a severe infusion reaction and emergency medical services. Monitor patient during the infusion and then observe for at ≥1 hour after the infusion is completed. 	<ul style="list-style-type: none"> Drug-drug interactions are unlikely between CAS plus IMD and medications that are renally excreted or that are CYP substrates, inhibitors, or inducers. 	<ul style="list-style-type: none"> To date, there are insufficient data for the Panel to recommend either for or against the use of CAS plus IMD for the treatment of outpatients with mild to moderate COVID-19. Patients who are hospitalized for COVID-19 should not receive CAS plus IMD outside of a clinical trial. A list of clinical trials is available: Casirivimab plus Imdevimab <p>Availability:</p> <ul style="list-style-type: none"> CAS plus IMD is available through the FDA EUA for high-risk outpatients with mild to moderate COVID-19.² See Anti-SARS-CoV-2 Monoclonal Antibodies for a list of high-risk conditions.
COVID-19 Convalescent Plasma				
<p>1 or more transfusions based on patient response</p>	<ul style="list-style-type: none"> TRALI TACO Allergic reactions Anaphylactic reactions Febrile nonhemolytic reactions Hemolytic reactions Hypothermia Metabolic complications Transmission of infectious pathogens³ Thrombotic events 	<ul style="list-style-type: none"> Before administering convalescent plasma to patients with a history of severe allergic or anaphylactic transfusion reactions, the Panel recommends consulting a transfusion medicine specialist who is associated with the hospital blood bank. Monitor for transfusion-related reactions. 	<ul style="list-style-type: none"> Drug products should not be added to the IV infusion line for the blood product. 	<ul style="list-style-type: none"> There are insufficient data for the Panel to recommend either for or against the use of COVID-19 convalescent plasma for the treatment of COVID-19. A list of clinical trials is available: COVID-19 Convalescent Plasma

Dosing Regimens	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
COVID-19 Convalescent Plasma , continued				
	<ul style="list-style-type: none"> Theoretical risk of antibody-mediated enhancement of infection and suppressed long-term immunity 	<ul style="list-style-type: none"> Monitor patient's vital signs at baseline and during and after transfusion. 		
SARS-CoV-2 Specific Immunoglobulin				
Dose varies by clinical trial	<ul style="list-style-type: none"> TRALI TACO Allergic reactions Antibody-mediated enhancement of infection Red blood cell alloimmunization Transmission of infectious pathogens 	<ul style="list-style-type: none"> Monitor for transfusion-related reactions. Monitor patient's vital signs at baseline and during and after transfusion. 	<ul style="list-style-type: none"> Drug products should not be added to the IV infusion line for the blood product. 	<ul style="list-style-type: none"> To date, there are insufficient data for the Panel to recommend either for or against the use of SARS-CoV-2 immunoglobulins for the treatment of COVID-19. A list of clinical trials is available: SARS-CoV-2 Immunoglobulin

Key: AE = adverse event; BAM = bamlanivimab; CAS = casirivimab; CYP = cytochrome P450; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; IMD = imdevimab; IV = intravenous; the Panel = the COVID-19 Treatment Guidelines Panel; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TACO = transfusion-associated circulatory overload; TRALI = transfusion-related acute lung injury

References

1. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of bamlanivimab. 2020. Available at: <https://www.fda.gov/media/143603/download>. Accessed November 13, 2020.
2. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of casirivimab and imdevimab. 2020. Available at: <https://www.fda.gov/media/143892/download>. Accessed November 13, 2020.
3. Marano G, Vaglio S, Pupella S, et al. Convalescent plasma: new evidence for an old therapeutic tool? *Blood Transfus*. 2016;14(2):152-157. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26674811>.

Cell-Based Therapy Under Evaluation for the Treatment of COVID-19

Last Updated: February 11, 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 cell-mediated inflammatory response induced by severe acute respiratory syndrome coronavirus 2 (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 are approved by the Food and Drug Administration (FDA) for the treatment of COVID-19. There are insufficient data 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 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-MS) 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-MSs, it was not possible to randomize the participants as originally planned. Among the 41 patients eligible to participate in the study, 12 received hUC-MS 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-MS 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

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 group died versus 24 patients (54.5%) in the control group. The 5-year follow-up was limited to five patients in the mesenchymal stem cell group. No safety concerns were identified.⁹

Clinical Trials

See [ClinicalTrials.gov](https://clinicaltrials.gov) 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 failure of the cells to work as expected, 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.¹⁰

Considerations in Pregnancy

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

Considerations in Children

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

References

1. Samsonraj RM, Raghunath M, Nurcombe V, Hui JH, van Wijnen AJ, Cool SM. Concise review: multifaceted characterization of human mesenchymal stem cells for use in regenerative medicine. *Stem Cells Transl Med.* 2017;6(12):2173-2185. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29076267>.

2. Li N, Hua J. Interactions between mesenchymal stem cells and the immune system. *Cell Mol Life Sci*. 2017;74(13):2345-2360. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28214990>.
3. Food and Drug Administration. FDA warns about stem cell therapies. 2019. Available at: <https://www.fda.gov/consumers/consumer-updates/fda-warns-about-stem-cell-therapies>. Accessed January 26, 2021.
4. Food and Drug Administration. Approved cellular and gene therapy products. 2019. Available at: <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products>. Accessed January 26, 2021.
5. Lukomska B, Stanaszek L, Zuba-Surma E, Legosz P, Sarzynska S, Drela K. Challenges and controversies in human mesenchymal stem cell therapy. *Stem Cells Int*. 2019. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31093291>.
6. Shetty AK. Mesenchymal stem cell infusion shows promise for combating coronavirus (COVID-19)-induced pneumonia. *Aging Dis*. 2020;11(2):462-464. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32257554>.
7. Leng Z, Zhu R, Hou W, et al. Transplantation of ACE2(-) mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia. *Aging Dis*. 2020;11(2):216-228. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32257537>.
8. Shu L, Niu C, Li R, et al. Treatment of severe COVID-19 with human umbilical cord mesenchymal stem cells. *Stem Cell Res Ther*. 2020;11(1):361. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32811531>.
9. Chen J, Hu C, Chen L, et al. Clinical study of mesenchymal stem cell treating acute respiratory distress syndrome induced by epidemic Influenza A (H7N9) infection, a hint for COVID-19 treatment. *Engineering (Beijing)*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32292627>.
10. Centers for Disease Control and Prevention. Stem cell and exosome products. 2019. Available at: <https://www.cdc.gov/hai/outbreaks/stem-cell-products.html>. Accessed January 26, 2021.

Immunomodulators Under Evaluation for the Treatment of COVID-19

Last Updated: February 11, 2021

Summary Recommendations
<p>See Therapeutic Management of Patients with COVID-19 for the COVID-19 Treatment Guidelines Panel's (the Panel's) recommendations on the use of the following:</p> <ul style="list-style-type: none">• Dexamethasone (or other corticosteroids) with or without remdesivir• Baricitinib with remdesivir. <p>See additional recommendations on the use of baricitinib below.</p> <p>See Statement on the Use of Tocilizumab (and Other Interleukin-6 Inhibitors) for the Panel's recommendations on the use of tocilizumab and sarilumab.</p> <p>Other Immunomodulators</p> <p>There are insufficient data for the Panel to recommend either for or against the use of the following immunomodulators for the treatment of COVID-19:</p> <ul style="list-style-type: none">• Baricitinib in combination with corticosteroids. Because both agents are potent immunosuppressants, there is potential for an additive risk of infection.• Baricitinib in combination with remdesivir for hospitalized COVID-19 patients when corticosteroids can be used• Interleukin (IL)-1 inhibitors (e.g., anakinra)• Interferon beta for the treatment of early (i.e., <7 days from symptom onset) mild to moderate COVID-19 <p>The Panel recommends against the use of the following immunomodulators for the treatment of COVID-19, except in a clinical trial:</p> <ul style="list-style-type: none">• Siltuximab, an anti-IL-6 monoclonal antibody (AIII)• Baricitinib without remdesivir (AIII)• Interferons (alfa or beta) for the treatment of severely or critically ill patients with COVID-19 (AIII)• Kinase inhibitors:<ul style="list-style-type: none">• Bruton's tyrosine kinase inhibitors (e.g., acalabrutinib, ibrutinib, zanubrutinib) (AIII)• Janus kinase inhibitors other than baricitinib (e.g., ruxolitinib, tofacitinib) (AIII)• Non-SARS-CoV-2-specific intravenous immune globulin (IVIG) (AIII). This recommendation should not preclude the use of IVIG when it is otherwise indicated for the treatment of complications that arise during the course of COVID-19.
<p>Rating of Recommendations: A = Strong; B = Moderate; C = Optional</p> <p>Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion</p>

Corticosteroids

Last Updated: November 3, 2020

Patients with severe COVID-19 can develop a systemic inflammatory response that can lead to lung injury and multisystem organ dysfunction. It has been proposed that the potent anti-inflammatory effects of corticosteroids might prevent or mitigate these deleterious effects. The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial, a multicenter, randomized, open-label trial in hospitalized patients with COVID-19, showed that the mortality from COVID-19 was lower among patients who were randomized to receive dexamethasone than among those who received the standard of care.¹ Details of the RECOVERY trial are discussed in [Table 4a](#).¹

The safety and efficacy of combination therapy of corticosteroids and an antiviral agent targeting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) for the treatment of COVID-19 have not been rigorously studied in clinical trials. However, there are theoretical reasons that such combination therapy may be beneficial in patients with severe disease. See [Therapeutic Management of Patients with COVID-19](#) for the Panel's recommendations on use of dexamethasone with or without remdesivir in certain hospitalized patients.

Rationale for Use of Corticosteroids in Patients With COVID-19

Both beneficial and deleterious clinical outcomes have been reported with use of corticosteroids (mostly prednisone or methylprednisolone) in patients with other pulmonary infections. In patients with *Pneumocystis jirovecii* pneumonia and hypoxia, prednisone therapy reduced the risk of death;² however, in outbreaks of other novel coronavirus infections (i.e., Middle East respiratory syndrome [MERS] and severe acute respiratory syndrome [SARS]), corticosteroid therapy was associated with delayed virus clearance.^{3,4} In severe pneumonia caused by influenza viruses, corticosteroid therapy appears to result in worse clinical outcomes, including secondary bacterial infection and death.⁵

Corticosteroids have been studied in critically ill patients with acute respiratory distress syndrome (ARDS) with conflicting results.⁶⁻⁸ Seven randomized controlled trials that included a total of 851 patients evaluated use of corticosteroids in patients with ARDS.⁷⁻¹³ A meta-analysis of these trial results demonstrated that, compared with placebo, corticosteroid therapy reduced the risk of all-cause mortality (risk ratio 0.75; 95% CI, 0.59–0.95) and duration of mechanical ventilation (mean difference, -4.93 days; 95% CI, -7.81 to -2.06 days).^{14,15}

Recommendations on the use of corticosteroids for COVID-19 are largely based on data from the RECOVERY trial, a large, multicenter, randomized, open-label trial performed in the United Kingdom. This trial compared hospitalized patients who received up to 10 days of dexamethasone to those who received the standard of care. Mortality at 28 days was lower among patients who were randomized to receive dexamethasone than among those who received the standard of care.¹ This benefit was observed in patients who were mechanically ventilated or required supplemental oxygen at enrollment. No benefit of dexamethasone was seen in patients who did not require supplemental oxygen at enrollment. Details of the RECOVERY trial are discussed in [Table 4a](#).¹

Corticosteroids used in various formulations and doses and for varying durations in patients with COVID-19 were also studied in several smaller randomized controlled trials.¹⁶⁻²⁰ Some of these trials were stopped early due to under enrollment following the release of the results from the RECOVERY trial. Given that the sample size of many these trials was insufficient to assess efficacy, evidence to support the use of methylprednisolone and hydrocortisone for the treatment of COVID-19 is not as robust as that demonstrated for dexamethasone in the RECOVERY trial. Data from some of these

studies can be found in [Table 4a](#).

Corticosteroids Other Than Dexamethasone

- If dexamethasone is not available, alternative glucocorticoids such as prednisone, methylprednisolone, or hydrocortisone can be used.
- For these drugs, the total daily dose equivalencies to dexamethasone 6 mg (oral or intravenous [IV])²¹ are:
 - Prednisone 40 mg
 - Methylprednisolone 32 mg
 - Hydrocortisone 160 mg
- Half-life, duration of action, and frequency of administration vary among corticosteroids.
 - *Long-acting corticosteroid*: dexamethasone; half-life: 36 to 72 hours, administer once daily.
 - *Intermediate-acting corticosteroids*: prednisone and methylprednisolone; half-life: 12 to 36 hours, administer once daily or in two divided doses daily.
 - *Short-acting corticosteroid*: hydrocortisone; half-life: 8 to 12 hours, administer in two to four divided doses daily.
- Hydrocortisone is commonly used to manage septic shock in patients with COVID-19; see [Care of Critically Ill Patients With COVID-19](#) for more information. Unlike other corticosteroids previously studied in patients with ARDS, dexamethasone lacks mineralocorticoid activity and thus has minimal effect on sodium balance and fluid volume.¹⁰

Monitoring, Adverse Effects, and Drug-Drug Interactions

- Clinicians should closely monitor patients with COVID-19 who are receiving dexamethasone for adverse effects (e.g., hyperglycemia, secondary infections, psychiatric effects, avascular necrosis).
- Prolonged use of systemic corticosteroids may increase the risk of reactivation of latent infections (e.g., hepatitis B virus [HBV], herpesvirus infections, strongyloidiasis, tuberculosis).
- The risk of reactivation of latent infections for a 10-day course of dexamethasone (6 mg once daily) is not well-defined. When initiating dexamethasone, appropriate screening and treatment to reduce the risk of *Strongyloides* hyperinfection in patients at high risk of strongyloidiasis (e.g., patients from tropical, subtropical, or warm, temperate regions or those engaged in agricultural activities)²²⁻²⁴ or fulminant reactivations of HBV²⁵ should be considered.
- Dexamethasone is a moderate cytochrome P450 (CYP) 3A4 inducer. As such, it may reduce the concentration and potential efficacy of concomitant medications that are CYP3A4 substrates. Clinicians should review a patient's medication regimen to assess potential interactions.
- Coadministration of remdesivir and dexamethasone has not been formally studied, but a clinically significant pharmacokinetic interaction is not predicted.
- Dexamethasone should be continued for up to 10 days or until hospital discharge, whichever comes first.

Considerations in Pregnancy

A short course of betamethasone and dexamethasone, which are known to cross the placenta, is routinely used to decrease neonatal complications of prematurity in women with threatened preterm delivery.^{26,27}

Given the potential benefit of decreased maternal mortality and the low risk of fetal adverse effects for a short course of dexamethasone therapy, the Panel recommends using **dexamethasone** in hospitalized pregnant women with COVID-19 who are mechanically ventilated (**AIII**) or who require supplemental oxygen but who are not mechanically ventilated (**BIII**).

Considerations in Children

The safety and effectiveness of dexamethasone or other corticosteroids for COVID-19 treatment have not been sufficiently evaluated in pediatric patients. Importantly, the RECOVERY trial did not include a significant number of pediatric patients, and mortality from COVID-19 is significantly lower among pediatric patients than among adult patients. Thus, caution is warranted when extrapolating the results of the RECOVERY trial to patients aged <18 years. Dexamethasone may be beneficial in pediatric patients with COVID-19 respiratory disease who require mechanical ventilation. Use of dexamethasone in patients who require other forms of supplemental oxygen support should be considered on a case-by-case basis and is generally not recommended for pediatric patients who require only low levels of oxygen support (i.e., nasal cannula only). Additional studies are needed to evaluate the use of steroids for the treatment of COVID-19 in pediatric patients, including for multisystem inflammatory syndrome in children (MIS-C).

Clinical Trials

Several clinical trials to evaluate corticosteroids for the treatment of COVID-19 are currently underway or in development. Please see [ClinicalTrials.gov](https://www.clinicaltrials.gov) for the latest information.

References

1. Recovery Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with COVID-19 - preliminary report. *N Engl J Med*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32678530>.
2. Bozzette SA, Sattler FR, Chiu J, et al. A controlled trial of early adjunctive treatment with corticosteroids for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. California Collaborative Treatment Group. *N Engl J Med*. 1990;323(21):1451-1457. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/2233917>.
3. Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid therapy for critically ill patients with Middle East Respiratory Syndrome. *Am J Respir Crit Care Med*. 2018;197(6):757-767. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29161116>.
4. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Med*. 2006;3(9):e343. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16968120>.
5. Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, Lim WS. Corticosteroids as adjunctive therapy in the treatment of influenza. *Cochrane Database Syst Rev*. 2016;3:CD010406. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26950335>.
6. Meduri GU, Bridges L, Shih MC, Marik PE, Siemieniuk RAC, Kocak M. Prolonged glucocorticoid treatment is associated with improved ARDS outcomes: analysis of individual patients' data from four randomized trials and trial-level meta-analysis of the updated literature. *Intensive Care Med*. 2016;42(5):829-840. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26508525>.
7. Meduri GU, Golden E, Freire AX, et al. Methylprednisolone infusion in early severe ARDS: results of a randomized controlled trial. *Chest*. 2007;131(4):954-963. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17426195>.
8. Steinberg KP, Hudson LD, Goodman RB, et al. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med*. 2006;354(16):1671-1684. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/16625008>.

9. Liu L, Li J, Huang YZ, et al. [The effect of stress dose glucocorticoid on patients with acute respiratory distress syndrome combined with critical illness-related corticosteroid insufficiency]. *Zhonghua Nei Ke Za Zhi*. 2012;51(8):599-603. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23158856>.
10. Villar J, Ferrando C, Martinez D, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. *Lancet Respir Med*. 2020;8(3):267-276. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32043986>.
11. Rezk NA, Ibrahim AM. Effects of methyl prednisolone in early ARDS. *Egypt J Chest Dis Tuberc*. 2013;62(1):167-172. Available at: <https://www.sciencedirect.com/science/article/pii/S0422763813000265>.
12. Tongyoo S, Permpikul C, Mongkolpun W, et al. Hydrocortisone treatment in early sepsis-associated acute respiratory distress syndrome: results of a randomized controlled trial. *Crit Care*. 2016;20(1):329. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27741949>.
13. Zhao WB, Wan SX, Gu DF, Shi B. Therapeutic effect of glucocorticoid inhalation for pulmonary fibrosis in ARDS patients. *Med J Chinese PLA*. 2014;39(9):741-745. Available at: <http://www.plamj.org/index.php/plamj/article/view/1009>.
14. Mammen MJ, Aryal K, Alhazzani W, Alexander PE. Corticosteroids for patients with acute respiratory distress syndrome: a systematic review and meta-analysis of randomized trials. *Pol Arch Intern Med*. 2020;130(4):276-286. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32186831>.
15. Alhazzani W, Moller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). *Crit Care Med*. 2020;48(6):e440-e469. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32224769>.
16. Jeronimo CMP, Farias MEL, Val FFA, et al. Methylprednisolone as adjunctive therapy for patients hospitalized with COVID-19 (Metcovid): a randomised, double-blind, phase IIb, placebo-controlled trial. *Clin Infect Dis*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32785710>.
17. Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. *JAMA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32876695>.
18. Dequin PF, Heming N, Meziani F, et al. Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19: a randomized clinical trial. *JAMA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32876689>.
19. Writing Committee for the R-CAPI, Angus DC, Derde L, et al. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: the REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. *JAMA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32876697>.
20. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32876694>.
21. Czock D, Keller F, Rasche FM, Haussler U. Pharmacokinetics and pharmacodynamics of systemically administered glucocorticoids. *Clin Pharmacokinet*. 2005;44(1):61-98. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15634032>.
22. Centers for Disease Control and Prevention. Parasites - strongyloides: resources for health professionals. 2020; https://www.cdc.gov/parasites/strongyloides/health_professionals/index.html. Accessed October 30, 2020.
23. Lier AJ, Tuan JL, Davis MW, et al. Case report: disseminated strongyloidiasis in a patient with COVID-19. *Am J Trop Med Hyg*. 2020. Available at: <http://www.ajtmh.org/docserver/fulltext/14761645/103/4/tpmd200699.pdf?expires=1606941469&id=id&accname=guest&checksum=9728AC8BEDF3E8369A7D3E6C2AFEB27E>.

24. Stauffer WM, Alpern JD, Walker PF. COVID-19 and dexamethasone: a potential strategy to avoid steroid-related strongyloides hyperinfection. *JAMA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32761166>.
25. Liu J, Wang T, Cai Q, et al. Longitudinal changes of liver function and hepatitis B reactivation in COVID-19 patients with pre-existing chronic HBV infection. *Hepatol Res*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32761993>.
26. Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. *Pediatrics*. 1972;50(4):515-525. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/4561295>.
27. Gyamfi-Bannerman C, Thom EA, Blackwell SC, et al. Antenatal betamethasone for women at risk for late preterm delivery. *N Engl J Med*. 2016;374(14):1311-1320. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26842679>.

Table 4a. Corticosteroids: Selected Clinical Data

Last Updated: February 11, 2021

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

Study Design	Methods	Results	Limitations and Interpretation
Dexamethasone in Hospitalized Patients With COVID-19—Preliminary Report (RECOVERY Trial)¹			
<p>Multi-center, randomized open-label adaptive trial in hospitalized patients with suspected or confirmed COVID-19 (n = 6,425)</p> <p>Country: United Kingdom</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> Hospitalization with clinically suspected or laboratory-confirmed SARS-CoV-2 infection <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> Physician determination that risks of participation too great based on patient’s medical history or an indication for corticosteroid therapy outside of the study <p>Interventions:</p> <ul style="list-style-type: none"> Patients randomized 2:1 to receive: <ul style="list-style-type: none"> Dexamethasone 6 mg PO or IV once daily plus SOC for up to 10 days or until hospital discharge, whichever came first, <i>or</i> SOC alone <p>Primary Endpoint:</p> <ul style="list-style-type: none"> All-cause mortality at 28 days after randomization 	<p>Number of Participants:</p> <ul style="list-style-type: none"> Dexamethasone plus SOC (n = 4,321) and SOC (n = 2,104) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> Mean age was 66 years. 64% of participants were men. 56% of participants had ≥1 comorbidity; 24% had diabetes. 89% of participants had laboratory-confirmed SARS-CoV-2 infection. At randomization, 16% of participants received invasive mechanical ventilation or ECMO, 60% required supplemental oxygen but not invasive ventilation, and 24% required no oxygen supplementation. 0% to 3% of the participants in both arms received RDV, HCQ, LPV/RTV, or tocilizumab; approximately 8% of participants in SOC alone arm received dexamethasone after randomization. <p>Outcomes:</p> <ul style="list-style-type: none"> 28-day mortality was 22.9% in dexamethasone arm and 25.7% in SOC arm (age-adjusted rate ratio 0.83; 95% CI, 0.75–0.93; <i>P</i> < 0.001). 	<p>Limitations:</p> <ul style="list-style-type: none"> Open label study This preliminary study analysis did not include the results for key secondary endpoints (e.g., cause-specific mortality, need for renal replacement), AEs, and the efficacy of dexamethasone in key subgroups (e.g., patients with comorbidities). Study participants with COVID-19 who required oxygen (but not mechanical ventilation) had variable disease severity; it is unclear whether all patients in this heterogeneous group derived benefit from dexamethasone, or whether benefit is restricted to those requiring higher levels of supplemental oxygen or oxygen delivered through a high-flow device. The age distribution of participants differed by respiratory status at randomization. The survival benefit of dexamethasone for mechanically ventilated patients aged >80 years is unknown because only 1% of the participants in this group were ventilated.

Study Design	Methods	Results	Limitations and Interpretation
Dexamethasone in Hospitalized Patients With COVID-19—Preliminary Report (RECOVERY Trial)¹, continued			
		<ul style="list-style-type: none"> The treatment effect of dexamethasone varied by baseline severity of COVID-19. Survival benefit appeared greatest among participants who required invasive mechanical ventilation at randomization. Among these participants, 28-day mortality was 29.3% in dexamethasone arm vs. 41.4% in SOC arm (rate ratio 0.64; 95% CI, 0.51–0.81). Among patients who required supplemental oxygen but not mechanical ventilation at randomization, 28-day mortality was 23.3% in dexamethasone arm vs. 26.2% in SOC arm (rate ratio 0.82; 95% CI, 0.72–0.94). No survival benefit in participants who did not require oxygen therapy at enrollment. Among these participants, 28-day mortality was 17.8% in dexamethasone arm vs. 14.0% in SOC arm (rate ratio 1.19; 95% CI, 0.91–1.55). 	<ul style="list-style-type: none"> It is unclear whether younger patients were more likely to receive mechanical ventilation than patients aged >80 years, given similar disease severity at baseline, with older patients preferentially assigned to oxygen therapy. The high baseline mortality of this patient population may limit generalizability of the study results to populations with a lower baseline mortality. <p>Interpretation:</p> <ul style="list-style-type: none"> In hospitalized patients with severe COVID-19 who required oxygen support, using dexamethasone 6 mg daily for up to 10 days reduced mortality at 28 days, with the greatest benefit seen in those who were mechanically ventilated at baseline. There was no observed survival benefit of dexamethasone in patients who did not require oxygen support at baseline.
Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-Analysis (REACT Working Group)²			
<p>Meta-analysis of 7 RCTs of corticosteroids in critically ill patients with COVID-19 (n = 1,703)</p> <p>Countries: Multinational</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> RCTs evaluating corticosteroids in critically ill patients with COVID-19 (identified via comprehensive search of ClinicalTrials.gov, Chinese Clinical Trial Registry, and EU Clinical Trials Register) 	<p>Number of Participants:</p> <ul style="list-style-type: none"> Corticosteroids (n = 678) and usual care or placebo (n = 1,025) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> Median age was 60 years. 29% of patients were women. 1,559 patients (91.5%) were on mechanical ventilation. 	<p>Limitations:</p> <ul style="list-style-type: none"> The design of the trials included in the meta-analysis differed in several ways, including the following: <ul style="list-style-type: none"> Definition of critical illness Specific corticosteroid used Dose of corticosteroid Duration of corticosteroid treatment

Study Design	Methods	Results	Limitations and Interpretation
Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-Analysis (REACT Working Group)², continued			
	<p>Interventions:</p> <ul style="list-style-type: none"> • Corticosteroids (i.e., dexamethasone, hydrocortisone, methylprednisolone) • Usual care or placebo <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • All-cause mortality up to 30 days after randomization 	<ul style="list-style-type: none"> • 47% of patients were on vasoactive agents at randomization across the 6 trials that reported this information. <p>Outcomes:</p> <ul style="list-style-type: none"> • Mortality was assessed at 28 days in 5 trials, 21 days in 1 trial, and 30 days in 1 trial. • Reported all-cause mortality at 28 days: Death occurred in 222 of 678 patients (32.7%) in corticosteroids group vs. 425 of 1,025 patients (41.5%) in usual care or placebo group; summary OR 0.66 (95% CI, 0.53–0.82; $P < 0.001$). • The fixed-effect summary ORs for the association with all-cause mortality were: <ul style="list-style-type: none"> • Dexamethasone: OR 0.64 (95% CI, 0.50–0.82; $P < 0.001$) in 3 trials with 1,282 patients • Hydrocortisone: OR 0.69 (95% CI, 0.43–1.12; $P = 0.13$) in 3 trials with 374 patients. • Methylprednisolone: OR 0.91 (95% CI, 0.29–2.87; $P = 0.87$) in 1 trial with 47 patients • For patients on mechanical ventilation (n = 1,559): OR 0.69 (95% CI, 0.55–0.86), with mortality of 30% for corticosteroids vs. 38% for usual care or placebo • For patients not on mechanical ventilation (n = 144): OR 0.41 (95% CI, 0.19–0.88) with mortality of 23% for corticosteroids vs. 42% for usual care or placebo • Across the 6 trials that reported SAEs, 18.1% of patients randomized to corticosteroids and 23.4% randomized to usual care or placebo experienced SAEs. 	<ul style="list-style-type: none"> • Type of control group (i.e., usual care or placebo) • Reporting of SAEs • The RECOVERY trial accounted for 59% of the participants, and 3 trials enrolled <50 patients each. • Some studies confirmed SARS-CoV-2 infection for participant inclusion while others enrolled participants with either probable or confirmed infection. • Although the risk of bias was low in 6 of the 7 trials, it was assessed as “some concerns” for 1 trial (which contributed only 47 patients). <p>Interpretation:</p> <ul style="list-style-type: none"> • Systemic corticosteroids decrease 28-day mortality in critically ill patients with COVID-19 without safety concerns. • Most of the participants were from the RECOVERY trial, thus the evidence of benefit in the meta-analysis is strongest for dexamethasone, the corticosteroid used in the RECOVERY trial.

Study Design	Methods	Results	Limitations and Interpretation
Methylprednisolone as Adjunctive Therapy for Patients Hospitalized With COVID-19 (Metcovid): A Randomised, Double-Blind, Phase IIb, Placebo-Controlled Trial³			
<p>Randomized, double-blind, placebo-controlled, single-center study of short-course methylprednisolone in hospitalized patients with confirmed or suspected COVID-19 pneumonia (n = 416)</p> <p>Country: Brazil</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged ≥18 years • Suspected or confirmed COVID-19 • SpO₂ ≤94% on room air <i>or</i> while using supplementary oxygen <i>or</i> under invasive mechanical ventilation <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Hypersensitivity to methylprednisolone • Chronic use of corticosteroids or immunosuppressive agents • HIV, decompensated cirrhosis, chronic renal failure <p>Interventions:</p> <ul style="list-style-type: none"> • Methylprednisolone IV 0.5 mg/kg twice daily for 5 days • Placebo (saline) IV <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Mortality by Day 28 <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> • Early mortality at Days 7 and 14 • Need for mechanical ventilation by Day 7 • Need for insulin by Day 28 • Positive blood culture at Day 7, sepsis by Day 28 • Mortality by Day 28 in specified subgroups 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • mITT analysis (n = 393): Methylprednisolone (n = 194) and placebo (n = 199) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Mean age was 55 years. • 65% of patients were men. • 29% of patients had diabetes. • At enrollment, 34% of participants in each group required invasive mechanical ventilation; 51% in methylprednisolone group and 45% in placebo group required supplemental oxygen. • Median time from illness onset to randomization was 13 days (IQR 9–16). • None of the participants received anti-IL-6, anti-IL-1, RDV, or convalescent plasma. • Hydrocortisone use for shock among patients was 8.7% in methylprednisolone group and 7.0% in placebo group. <p>Primary Outcomes:</p> <ul style="list-style-type: none"> • No difference in 28-day mortality: 37.1% in methylprednisolone arm vs. 38.2% in placebo arm (HR 0.92; 95% CI, 0.67–1.28; <i>P</i> = 0.63). <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> • No difference between groups in early mortality at Day 7 (HR 0.68; 95% CI, 0.43–1.06) or Day 14 (HR 0.82; 95% CI, 0.57–1.18) • No difference in need for mechanical ventilation by Day 7: 19.4% of methylprednisolone recipients vs. 16.8% of placebo recipients (<i>P</i> = 0.65) 	<p>Limitations:</p> <ul style="list-style-type: none"> • The median days from illness onset to randomization was longer than in other corticosteroid studies. • The high baseline mortality of this patient population may limit generalizability of the study results to populations with a lower baseline mortality. <p>Interpretation:</p> <ul style="list-style-type: none"> • Use of weight-based methylprednisolone for 5 days did not reduce overall 28-day mortality. • In a post hoc subgroup analysis, mortality among those aged >60 years was lower in the methylprednisolone group than in the placebo group.

Study Design	Methods	Results	Limitations and Interpretation
Methylprednisolone as Adjunctive Therapy for Patients Hospitalized With COVID-19 (Metcovid): A Randomised, Double-Blind, Phase IIb, Placebo-Controlled Trial³, continued			
		<ul style="list-style-type: none"> • No significant difference between the methylprednisolone and placebo groups in need for insulin (59.5% vs. 49.4% of patients), positive blood cultures at Day 7 (8.3% vs. 8.0% of patients), or sepsis by Day 28 (38.1% vs. 38.7% of patients) • In post hoc analysis, 28-day mortality in participants aged >60 years was lower in methylprednisolone group than in placebo group (46.6% vs. 61.9%; HR 0.63; 95% CI, 0.41–0.98). 	
Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial⁴			
<p>Multicenter, randomized, clinical trial in patients with COVID-19 and moderate to severe ARDS (n = 299) Country: Brazil</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged ≥18 years • Confirmed or suspected COVID-19 • On mechanical ventilation within 48 hours of meeting criteria for moderate to severe ARDS with PaO₂/FiO₂ ≤200 mm Hg <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Recent corticosteroid use • Use of immunosuppressive drugs in the past 21 days • Expected death in next 24 hours <p>Interventions:</p> <ul style="list-style-type: none"> • Dexamethasone 20 mg IV daily for 5 days, then 10 mg IV daily for 5 days or until ICU discharge plus SOC • SOC alone 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • ITT analysis (n = 299): Dexamethasone plus SOC (n = 151) and SOC alone (n = 148) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Dexamethasone group included more women than the SOC group (40% vs. 35%), more patients with obesity (31% vs. 24%), and fewer patients with diabetes (38% vs. 47%). • Other baseline characteristics were similar for the dexamethasone and SOC groups: <ul style="list-style-type: none"> • Mean age was 60 vs. 63 years; vasopressor use by 66% vs. 68% of patients; mean PaO₂/FiO₂ of 131 mm Hg vs. 133 mm Hg. • Median time from symptom onset to randomization was 9–10 days. • Median time from mechanical ventilation to randomization was 1 day. • No patients received RDV; anti-IL-6 and convalescent plasma were not widely available. • Median duration of dexamethasone therapy was 10 days (IQR 6–10 days). 	<p>Limitations:</p> <ul style="list-style-type: none"> • Open-label study • The study was underpowered to assess some outcomes because it stopped enrollment after data from the RECOVERY trial were released. • During the study, 35% of the patients in the SOC group received corticosteroids for shock, bronchospasm, or other reasons. • Patients who were discharged from the hospital before 28 days were not followed for rehospitalization or mortality. • The high baseline mortality of the patient population may limit generalizability of the study results to populations with a lower baseline mortality. <p>Interpretation:</p> <ul style="list-style-type: none"> • Compared with SOC alone, dexamethasone at a higher dose than used in the RECOVERY trial plus SOC

Study Design	Methods	Results	Limitations and Interpretation
Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial⁴, continued			
	<p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Mean number of days alive and free from mechanical ventilation by Day 28 <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> • All-cause mortality at Day 28 • ICU-free days by Day 28 • Duration of mechanical ventilation by Day 28 • Score on 6-point WHO ordinal scale at Day 15 • SOFA score at 7 days • Components of the primary outcome or in the outcome of discharged alive within 28 days 	<ul style="list-style-type: none"> • 35% of patients in SOC alone group also received corticosteroids. <p>Primary Outcomes:</p> <ul style="list-style-type: none"> • The mean number of days alive and free from mechanical ventilation by Day 28 was higher in the dexamethasone group than in the SOC group (6.6 vs. 4.0 days, estimated difference of 2.3 days; 95% CI, 0.2–4.4; $P = 0.04$). <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> • There were no differences between the dexamethasone and SOC groups for the following outcomes: <ul style="list-style-type: none"> • All-cause mortality at Day 28 (56.3% vs. 61.5%; HR 0.97; 95% CI, 0.72–1.31; $P = 0.85$) • ICU-free days by Day 28 (mean of 2.1 vs. 2.0 days; $P = 0.50$) • Duration of mechanical ventilation by Day 28 (mean of 12.5 vs. 13.9 days; $P = 0.11$) • Score on 6-point WHO ordinal scale at Day 15 (median score of 5 for both groups) • The mean SOFA score at 7 days was lower in the dexamethasone group than in the SOC group (6.1 vs. 7.5, difference -1.16; 95% CI, -1.94 to -0.38; $P = 0.004$). • The following safety outcomes were comparable for dexamethasone and SOC groups: need for insulin (31.1% vs. 28.4%), new infections (21.9% vs. 29.1%), bacteremia (7.9% vs. 9.5%), and other SAEs (3.3% vs. 6.1%). • In post hoc analysis, the dexamethasone group had a lower cumulative probability of death or mechanical ventilation at Day 15 than the SOC group (67.5% vs. 80.4%; OR 0.46; 95% CI, 0.26–0.81; $P = 0.01$). 	<p>increased the number of days alive and free of mechanical ventilation over 28 days of follow-up in patients with COVID-19 and moderate to severe ARDS.</p> <ul style="list-style-type: none"> • Dexamethasone was not associated with an increased risk of AEs in this population. • More than one-third of those randomized to the standard care alone group also received corticosteroids; it is impossible to determine the effect of corticosteroid use in these patients on the overall study outcomes.

Study Design	Methods	Results	Limitations and Interpretation
Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19: A Randomized Clinical Trial⁵			
<p>Multicenter, randomized, double-blind, sequential trial in patients with confirmed or suspected COVID-19 and acute respiratory failure (n = 149)</p> <p>Country: France</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged ≥18 years • Confirmed SARS-CoV-2 infection or radiographically suspected COVID-19, with at least 1 of 4 severity criteria: <ul style="list-style-type: none"> • Need for mechanical ventilation with PEEP ≥5 cm H₂O • High-flow oxygen with PaO₂/FiO₂ <300 mm Hg and FiO₂ ≥50% • Reservoir mask oxygen with PaO₂/FiO₂ <300 mm Hg (estimated) • Pneumonia severity index >130 (scoring table) <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Septic shock • Do-not-intubate orders <p>Interventions:</p> <ul style="list-style-type: none"> • Continuous infusion hydrocortisone 200 mg/day until Day 7, then hydrocortisone 100 mg/day for 4 days, and then hydrocortisone 50 mg/day for 3 days, for a total treatment duration of 14 days • Patients who showed clinical improvement by Day 4 were switched to a shorter 8-day regimen. 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • ITT analysis (n = 149 participants): Hydrocortisone (n = 76) and placebo (n = 73) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Mean age of participants was 62 years; 70% were men; median BMI was 28. • 96% of participants had confirmed SARS-CoV-2 infection. • Median symptom duration before randomization was 9 days in hydrocortisone group vs. 10 days in placebo group. • 81% of the patients overall were mechanically ventilated, and 24% in hydrocortisone group and 18% in placebo group were receiving vasopressors. • Among the patients receiving concomitant COVID-19 treatment, 3% received RDV, 14% LPV/RTV, 13% HCQ, and 34% HCQ plus AZM. • Median treatment duration was 10.5 days in hydrocortisone group vs. 12.8 days in placebo group (P = 0.25). <p>Primary Outcome:</p> <ul style="list-style-type: none"> • There was no difference in the proportion of patients with treatment failure by Day 21, which occurred in 32 of 76 patients (42.1%) in hydrocortisone group and 37 of 73 patients (50.7%) in placebo group (difference -8.6%; 95% CI, -24.9% to 7.7%; P = 0.29). <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> • There was no difference between the groups in the need for intubation, rescue strategies, or oxygenation (i.e., change in PaO₂/FiO₂). • Among the patients who did not require mechanical ventilation at baseline, 8 of 16 patients (50%) in hydrocortisone group required subsequent 	<p>Limitations:</p> <ul style="list-style-type: none"> • Small sample size. Planned sample size of 290, but 149 enrolled because study was terminated early after the release of results from the RECOVERY trial. • Limited information about comorbidities (e.g., hypertension) • Participants' race and/or ethnicity were not reported. • Nosocomial infections were recorded but not adjudicated. <p>Interpretation:</p> <ul style="list-style-type: none"> • Compared to placebo, hydrocortisone did not reduce treatment failure (defined as death or persistent respiratory support) at Day 21 in ICU patients with COVID-19 and acute respiratory failure. • Because this study was terminated early, it is difficult to make conclusions about the efficacy and safety of hydrocortisone therapy. • The starting dose of hydrocortisone used in this study were slightly higher than the 6 mg dose of dexamethasone used in the RECOVERY study. The hydrocortisone dose was adjusted according to clinical response.

Study Design	Methods	Results	Limitations and Interpretation
Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19: A Randomized Clinical Trial⁵, continued			
	<p>Primary Endpoint:</p> <ul style="list-style-type: none"> Treatment failure (defined as death or persistent dependency on mechanical ventilation or high-flow oxygen) by Day 21 <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> Need for intubation, rescue strategies, or oxygenation (i.e., change in PaO₂/FiO₂) Nosocomial infections on Day 28 Clinical status on Day 21 	<p>intubation vs. 12 of 16 (75%) in placebo group.</p> <ul style="list-style-type: none"> 3 SAEs were reported (cerebral vasculitis, cardiac arrest due to PE, and intra-abdominal hemorrhage from anticoagulation for PE); all occurred in the hydrocortisone group, but none were attributed to the intervention. There was no difference between the groups in proportion of patients with nosocomial infections on Day 28. In post hoc analysis, clinical status on Day 21 did not significantly differ between the groups except for fewer deaths in the hydrocortisone group (14.7% of patients died vs. 27.4% in placebo group; <i>P</i> = 0.06): By Day 21, 57.3% of patients in hydrocortisone group vs. 43.8% in placebo group were discharged from the ICU and 22.7% in hydrocortisone group vs. 23.3% in placebo group were still mechanically ventilated. 	
Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial (CAPE COD)⁶			
<p>Randomized, embedded, multifactorial, adaptive platform trial of patients with severe COVID-19 (n = 403)</p> <p>Countries: Multinational</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> Aged ≥18 years Presumed or confirmed SARS-CoV-2 infection ICU admission for respiratory or cardiovascular organ support <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> Presumed imminent death Systemic corticosteroid use >36 hours since ICU admission 	<p>Number of Participants:</p> <ul style="list-style-type: none"> mITT analysis (n = 384): Fixed-dose hydrocortisone (n=137), shock-based hydrocortisone (n = 146), and no hydrocortisone (n = 101) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> Mean age was 60 years. 71% of patients were men. Mean BMI was 29.7–30.9. 50% to 64% of patients received mechanical ventilation. 	<p>Limitations:</p> <ul style="list-style-type: none"> Early termination following release of RECOVERY study results Randomized study, but open label <p>Interpretation:</p> <ul style="list-style-type: none"> Corticosteroids did not significantly increase support-free days in either the fixed-dose hydrocortisone or the shock-dependent hydrocortisone group, although the early termination of the trial led to limited power to detect difference between the study arms.

Study Design	Methods	Results	Limitations and Interpretation
Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial (CAPE COD)⁶, continued			
	<p>Interventions:</p> <ul style="list-style-type: none"> • Hydrocortisone 50 mg 4 times daily for 7 days • Septic shock-based hydrocortisone 50 mg 4 times daily for the duration of shock • No hydrocortisone <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Days free of respiratory and cardiovascular organ support up to Day 21. (For this ordinal outcome, patients who died were assigned -1 day.) <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> • In-hospital mortality • SAEs 	<p>Primary Outcome:</p> <ul style="list-style-type: none"> • No difference between the groups in organ-support free-days at Day 21 (median of 0 days in each group). • Compared to the no hydrocortisone group, median adjusted OR for the primary outcome: <ul style="list-style-type: none"> • OR 1.43 (95% credible interval, 0.91–2.27) with 93% Bayesian probability of superiority for the fixed-dose hydrocortisone group • OR 1.22 (95% credible interval, 0.76–1.94) with 80% Bayesian probability of superiority for the shock-based hydrocortisone group <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> • No difference between the groups in mortality; 30%, 26%, and 33% of patients died in the fixed-dose, shock-based, and no hydrocortisone groups, respectively. • SAEs reported in 3%, 3%, and 1% of patients in the fixed-dose, shock-based, and no hydrocortisone groups, respectively. 	
Efficacy Evaluation of Early, Low-Dose, Short-Term Corticosteroids in Adults Hospitalized with Non-Severe COVID-19 Pneumonia: A Retrospective Cohort Study⁷			
<p>Retrospective cohort study in patients with nonsevere COVID-19 pneumonia and propensity score-matched controls (n = 55 matched case-control pairs)</p> <p>Country: China</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Confirmed COVID-19 • Pneumonia on chest CT scan • Aged ≥16 years <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Severe pneumonia defined as having any of the following: respiratory distress, respiratory rates >30 breaths/min, SpO₂ <93%, oxygenation index <300 mm Hg, mechanical ventilation, or shock 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • Corticosteroids (n = 55): IV methylprednisolone (n=50) and prednisone (n = 5) • No corticosteroids (n = 55 matched controls chosen from 420 patients who did not receive corticosteroids) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Median age was 58–59 years. • Median oxygen saturation was 95%. • 42% of patients in corticosteroids group and 46% in no corticosteroids group had comorbidities, including 35% to 36% with hypertension and 11% to 13% with diabetes. 	<p>Limitations:</p> <ul style="list-style-type: none"> • Retrospective, case-control study • Small sample size (55 case-control pairs) • Corticosteroid therapy was selected preferentially for patients who had more risk factors for severe progression of COVID-19; the propensity score matching may not have adjusted for some of the unmeasured confounders.

Study Design	Methods	Results	Limitations and Interpretation
Efficacy Evaluation of Early, Low-Dose, Short-Term Corticosteroids in Adults Hospitalized with Non-Severe COVID-19 Pneumonia: A Retrospective Cohort Study⁷, continued			
	<ul style="list-style-type: none"> • Immediate ICU admission upon hospitalization • Use of corticosteroids after progression to severe disease <p>Interventions:</p> <ul style="list-style-type: none"> • Early, low-dose corticosteroids: <ul style="list-style-type: none"> • IV methylprednisolone 20 mg/day or 40 mg/day for 3–5 days • PO prednisone 20 mg/day for 3 days • No corticosteroids <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Rates of severe disease and death <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> • Duration of fever • Virus clearance time • Length of hospital stay • Use of antibiotics 	<p>Primary Outcomes:</p> <ul style="list-style-type: none"> • 7 patients (12.7%) in the corticosteroids group developed severe disease vs. 1 (1.8%) in the no corticosteroids group ($P = 0.03$); time to severe disease: HR 2.2 (95% CI, 2.0–2.3; $P < 0.001$). • There was 1 death in the methylprednisolone group vs. none in the no corticosteroids group. <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> • Each of the following outcomes was longer in the corticosteroids group than in the no corticosteroids group ($P < 0.001$ for each outcome): duration of fever (5 vs. 3 days), virus clearance time (18 vs. 11 days), and length of hospital stay (23 vs. 15 days). • More patients in the corticosteroids group than in the no corticosteroids group were prescribed antibiotics (89% vs. 24%) and antifungal therapy (7% vs. 0%). 	<ul style="list-style-type: none"> • Selection bias in favor of the no corticosteroids group may have been introduced by excluding patients who used corticosteroids after progression to severe disease from the study. <p>Interpretation:</p> <ul style="list-style-type: none"> • In this nonrandomized, case-control study, methylprednisolone therapy in patients with nonsevere COVID-19 pneumonia was associated with worse outcomes, but this finding is difficult to interpret because of potential confounding factors. • It is unclear whether the results for methylprednisolone therapy can be generalized to therapy with other corticosteroids.

Key: AE = adverse event; ARDS = acute respiratory distress syndrome; AZM = azithromycin; BMI = body mass index; CT = computerized tomography; ECMO = extracorporeal membrane oxygenation; EU = European Union; HCQ = hydroxychloroquine; ICU = intensive care unit; IL = interleukin; ITT = intention-to-treat; IV = intravenous; LPV/RTV = lopinavir/ritonavir; mITT = modified intention-to-treat; the Panel = the COVID-19 Treatment Guidelines Panel; PaO₂/FiO₂ = ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; PE = pulmonary embolism; PEEP = positive end-expiratory pressure; PO = oral; RCT = randomized controlled trial; RDV = remdesivir; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOC = standard of care; SOFA = sequential organ failure assessment; SpO₂ = saturation of oxygen; WHO = World Health Organization

References

1. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with COVID-19—preliminary report. *N Engl J Med*. 2020;Published online ahead of print. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32678530>.
2. WHO Rapid Evidence Appraisal for COVID-19 Therapies Working Group, Sterne JAC, Murthy S, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA*. 2020;324(13):1330-1341. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32876694>.
3. Jeronimo CMP, Farias MEL, Val FFA, et al. Methylprednisolone as adjunctive therapy for patients hospitalized with COVID-19 (Metcovid): a randomised, double-blind, Phase IIb, placebo-controlled trial. *Clin Infect Dis*. 2020;Published online ahead of print. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32785710>.
4. Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. *JAMA*. 2020;324(13):1307-1316.. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32876695>.
5. Dequin PF, Heming N, Meziani F, et al. Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19: a randomized clinical trial. *JAMA*. 2020;324(13):1298-1306. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32876689>.
6. Angus DC, Derde L, Al-Beidh F, et al. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: The REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. *JAMA*. 2020;324(13):1317-1329. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32876697>.
7. Li Q, Li W, Jin Y, et al. Efficacy evaluation of early, low-dose, short-term corticosteroids in adults hospitalized with non-severe COVID-19 pneumonia: a retrospective cohort study. *Infect Dis Ther*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32880102>.

Interferons (Alfa, Beta)

Last Updated: August 27, 2020

Interferons are a family of cytokines with antiviral properties. They have been suggested as a potential treatment for COVID-19 because of their *in vitro* and *in vivo* antiviral properties.

Recommendation

The COVID-19 Treatment Guidelines Panel **recommends against** the use of interferons for the treatment of patients with severe or critical COVID-19, except in a clinical trial (**AIII**). There are insufficient data to recommend either for or against the use of **interferon beta** for the treatment of early (i.e., <7 days from symptom onset) mild and moderate COVID-19.

Rationale

Studies have shown no benefit of interferons in patients with other coronavirus infections (i.e., Middle East respiratory syndrome [MERS], severe acute respiratory syndrome [SARS]) who have severe or critical disease. In addition, interferons have significant toxicities that outweigh the potential for benefit. Interferons may have antiviral activity early in the course of infection. However, there is insufficient data to assess the potential benefit of interferon use during early disease versus the toxicity risks.

Clinical Data for COVID-19

Interferon Beta-1a

Press release, July 20, 2020: A double-blind, placebo-controlled trial conducted in the United Kingdom evaluated inhaled interferon beta-1a (once daily for up to 14 days) in nonventilated patients hospitalized with COVID-19. Compared to the patients receiving placebo (n = 50), the patients receiving inhaled interferon beta-1a (n = 48) were more likely to recover to ambulation without restrictions (HR 2.19; 95% CI, 1.03–4.69; P = 0.04), had decreased odds of developing severe disease (OR 0.21; 95% CI, 0.04–0.97; P = 0.046), and had less breathlessness. Additional detail is required to fully evaluate these findings and their implications. Of note, inhaled interferon beta-1a as used in this study is not commercially available in the United States.¹

Preprint manuscript posted online, July 13, 2020: An open-label, randomized trial at a single center in Iran evaluated subcutaneous interferon beta-1a (three times weekly for 2 weeks) in patients with severe COVID-19. There was no difference in the primary outcome of time to clinical response between the interferon beta-1a group (n = 42) and the control group (n = 39), and there was no difference between the groups in overall length of hospital stay, length of intensive care unit stay, or duration of mechanical ventilation. The reported 28-day overall mortality was lower in the interferon beta-1a group; however, four patients in the interferon beta-1a group who died before receiving the fourth dose of interferon beta-1a were excluded from the analysis, which makes it difficult to interpret these results.²

Combination of Interferon Beta-1b, Lopinavir/Ritonavir, and Ribavirin in the Treatment of Hospitalized Patients With COVID-19

An open-label, Phase 2 clinical trial randomized 127 participants (median age of 52 years) 2:1 to combination antiviral therapy or lopinavir/ritonavir. In the combination antiviral therapy group, the treatment regimen differed by time from symptom onset to hospital admission. Participants hospitalized within 7 days of symptom onset (n = 76) were randomized to triple drug therapy (interferon beta-1b 8 million units administered subcutaneously every other day for up to 7 days total, lopinavir/ritonavir,

and ribavirin); those hospitalized ≥ 7 days after symptom onset ($n = 51$) were randomized to double therapy (lopinavir/ritonavir and ribavirin) because of concerns regarding potential inflammatory effects of interferon. Patients in the control group received lopinavir/ritonavir alone regardless of the time from symptom onset to hospitalization. The study participants were patients in Hong Kong with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection who were hospitalized, regardless of disease severity, until they had two negative nasopharyngeal (NP) swab tests.

The time to a negative result on a polymerase chain reaction SARS-CoV-2 test on an NP swab (the primary endpoint) was shorter in the combination therapy group than in the control group (median of 7 days vs. 12 days; $P = 0.001$). The combination group had more rapid clinical improvement as assessed by the National Early Warning Score (NEWS) 2 and Sequential Organ Failure Assessment (SOFA) score and a shorter hospital stay (median of 9 days for the combination group vs. 14.5 days for the control group; $P = 0.016$). There was no difference in oxygen use between the groups. The antiviral and clinical effect was more pronounced in the patients hospitalized within 7 days of symptom onset, suggesting that interferon beta-1b with or without ribavirin was the critical component of the combination antiviral therapy. The study provides no information about the effect of interferon beta-1b when administered ≥ 7 days after symptom onset.³

Interferon Alfa-2b

In a retrospective cohort study of 77 adults with moderate COVID-19 in China, participants were treated with nebulized interferon alfa-2b, nebulized interferon alfa-2b with umifenovir, or umifenovir only. The time to viral clearance in the upper respiratory tract and reduction in systemic inflammation was faster in the interferon alfa-2b groups than in the umifenovir only group. However, the results of this study are difficult to interpret because participants in the interferon alfa-2b with umifenovir group were substantially younger than those in the umifenovir only group (mean age of 40 years in the interferon alfa-2b with umifenovir group vs. 65 years in the umifenovir only group) and had fewer comorbidities (15% in the interferon alfa-2b with umifenovir group vs. 54% in the umifenovir only group) at study entry. The nebulized interferon alfa-2b formulation is not approved by the Food and Drug Administration for use in the United States.⁴

Clinical Data for SARS and MERS

Interferon beta used alone and in combination with ribavirin in patients with SARS and MERS has failed to show a significant positive effect on clinical outcomes.⁵⁻⁹

In a retrospective observational analysis of 350 critically ill patients with MERS⁶ from 14 hospitals in Saudi Arabia, the mortality rate was higher among patients who received ribavirin and interferon (beta-1a, alfa-2a, or alfa-2b) than among those who did not receive either drug.

A randomized clinical trial that included 301 patients with acute respiratory distress syndrome¹⁰ found that intravenous interferon beta-1a had no benefit over placebo as measured by ventilator-free days over a 28-day period (median of 10.0 days in the interferon beta-1a group vs. 8.5 days in the placebo group) or mortality (26.4% in the interferon beta-1a group vs. 23.0% in the placebo group).

Clinical Trials

See [ClinicalTrials.gov](https://clinicaltrials.gov) for a list of [ongoing clinical trials for interferon and COVID-19](#).

Adverse Effects

The most frequent adverse effects of interferon alfa include flu-like symptoms, nausea, fatigue, weight loss, hematological toxicities, elevated transaminases, and psychiatric problems (e.g., depression and

suicidal ideation). Interferon beta is better tolerated than interferon alfa.^{11,12}

Drug-Drug Interactions

The most serious drug-drug interactions with interferons are the potential for added toxicity with concomitant use of other immunomodulators and chemotherapeutic agents.^{11,12}

Considerations in Pregnancy

Analysis of data from several large pregnancy registries did not demonstrate an association between exposure to interferon beta-1b preconception or during pregnancy and an increased risk of adverse birth outcomes (e.g., spontaneous abortion, congenital anomaly),^{13,14} and exposure did not influence birth weight, height, or head circumference.¹⁵

Considerations in Children

There are limited data on the use of interferons for the treatment of respiratory viral infections in children.

References

1. Synairgen announces positive results from trial of SNG001 in hospitalised COVID-19 patients [press release]. July 20, 2020. Available at: <https://www.synairgen.com/wp-content/uploads/2020/07/200720-Synairgen-announces-positive-results-from-trial-of-SNG001-in-hospitalised-COVID-19-patients.pdf>. Accessed August 24, 2020.
2. Davoudi-Monfared E, Rahmani H, Khalili H, et al. A randomized clinical trial of the efficacy and safety of interferon beta-1a in treatment of severe COVID-19. *Antimicrob Agents Chemother*. 2020;64(9):e01061-20. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32661006>.
3. 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. *Lancet*. 2020;395(10238):1695-1704. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32401715>.
4. Zhou Q, Chen V, Shannon CP, et al. Interferon-alpha2b treatment for COVID-19. *Front Immunol*. 2020;11:1061. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32574262>.
5. Al-Tawfiq JA, Momattin H, Dib J, Memish ZA. Ribavirin and interferon therapy in patients infected with the Middle East respiratory syndrome coronavirus: an observational study. *Int J Infect Dis*. 2014;20:42-46. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24406736>.
6. Arabi YM, Shalhoub S, Mandourah Y, et al. Ribavirin and interferon therapy for critically ill patients with Middle East respiratory syndrome: a multicenter observational study. *Clin Infect Dis*. 2020;70(9):1837-1844. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31925415>.
7. Chu CM, Cheng VC, Hung IF, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax*. 2004;59(3):252-256. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14985565>.
8. Omrani AS, Saad MM, Baig K, et al. Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: a retrospective cohort study. *Lancet Infect Dis*. 2014;14(11):1090-1095. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25278221>.
9. Shalhoub S, Farahat F, Al-Jiffri A, et al. IFN-alpha2a or IFN-beta1a in combination with ribavirin to treat Middle East respiratory syndrome coronavirus pneumonia: a retrospective study. *J Antimicrob Chemother*. 2015;70(7):2129-2132. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25900158>.
10. Ranieri VM, Pettila V, Karvonen MK, et al. Effect of intravenous interferon beta-1a on death and days free from mechanical ventilation among patients with moderate to severe acute respiratory distress syndrome: a randomized clinical trial. *JAMA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32065831>.

11. Interferon alpha-2b (Intron A) [package insert]. Food and Drug Administration. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103132Orig1s5199lbl.pdf.
12. Interferon beta-1a (Rebif) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/103780s5204lbl.pdf.
13. Sandberg-Wollheim M, Alteri E, Moraga MS, Kornmann G. Pregnancy outcomes in multiple sclerosis following subcutaneous interferon beta-1a therapy. *Mult Scler*. 2011;17(4):423-430. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21220368>.
14. Hellwig K, Duarte Caron F, Wicklein EM, Bhatti A, Adamo A. Pregnancy outcomes from the global pharmacovigilance database on interferon beta-1b exposure. *Ther Adv Neurol Disord*. 2020;13:1756286420910310. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32201504>.
15. Burkill S, Vattulainen P, Geissbuehler Y, et al. The association between exposure to interferon-beta during pregnancy and birth measurements in offspring of women with multiple sclerosis. *PLoS One*. 2019;14(12):e0227120. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31887199>.

Interleukin-1 Inhibitors

Last Updated: July 17, 2020

Recommendation

- There are insufficient data to recommend for or against the use of interleukin (IL)-1 inhibitors, such as **anakinra**, for the treatment of COVID-19.

Rationale

There are case series data but no clinical trial data on the use of IL-1 inhibitors in patients with COVID-19.

Anakinra is a recombinant human IL-1 receptor antagonist. It is approved by the Food and Drug Administration (FDA) to treat rheumatoid arthritis and cryopyrin-associated periodic syndromes, specifically neonatal-onset multisystem inflammatory disease.¹ It is also used off-label for severe chimeric antigen receptor T cell (CAR T-cell)-mediated cytokine release syndrome (CRS) and macrophage activation syndrome (MAS)/secondary hemophagocytic lymphohistiocytosis.

Rationale for Use in Patients with COVID-19

Endogenous IL-1 is elevated in patients with COVID-19 and other conditions, such as severe CAR T-cell-mediated CRS. Case reports and case series have described favorable responses to anakinra in patients with these syndromes, including a survival benefit in patients with sepsis and reversal of cytokine storm after tocilizumab failure in adults with MAS.^{2,3}

Clinical Data for COVID-19

- A case-control study compared outcomes in 52 consecutive patients with COVID-19 treated with anakinra and 44 historical controls. The patients in both groups were all admitted to the same hospital in Paris, France. Case patients were consecutive admissions from March 24 to April 6, 2020, with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or lung infiltrates on chest imaging typical of COVID-19, and either significant hypoxia ($\text{SpO}_2 \leq 93\%$ with $\geq 6\text{L}/\text{min O}_2$) or worsening hypoxia ($\text{SpO}_2 \leq 93\%$ with $>3\text{L}/\text{min O}_2$ and a loss of $\geq 3\%$ of O_2 saturation on room air in the previous 24 hours). The historic controls were patients who fulfilled the same eligibility criteria and admitted to the hospital during the same period. As standard of care for both groups, some patients received hydroxychloroquine, azithromycin, or parenteral beta-lactam antibiotics. Anakinra was dosed as 100 mg subcutaneous (SQ) twice daily for 72 hours, followed by anakinra 100 mg SQ daily for 7 days. Clinical characteristics were similar between the groups, except that the cases had a lower mean body mass index than the controls ($25.5 \text{ kg}/\text{m}^2$ vs. $29.0 \text{ kg}/\text{m}^2$, respectively), longer duration of symptoms (mean of 8.4 days for cases vs. 6.2 days for controls), and a higher frequency of hydroxychloroquine use (90% for cases vs. 61% for controls) and azithromycin use (49% for cases vs. 34% for controls). The primary outcome of admission to the intensive care unit for mechanical ventilation or death occurred among 13 case patients (25%) and 32 control patients (73%) (hazard ratio 0.22; 95% confidence interval, 0.11 to 0.41). However, within the first 2 days of follow up, in the control group, six patients (14%) had died and 19 patients (43%) had reached the composite primary outcome, which further limited intragroup comparisons and specifically analyses of time to event. C-reactive protein (CRP) levels decreased by Day 4 among those receiving anakinra. Thromboembolic events occurred in 10 patients (19%) who received anakinra and in five control patients (11%). The clinical implications of these findings are uncertain due to limitations in the

study design related to unmeasured confounding combined with the very high early event rate among the retrospective controls.⁴

- A single-center, retrospective cohort study compared outcomes in 29 patients following open-label use of anakinra to outcomes in 16 historical controls enrolled at the same medical center in Italy. All patients had COVID-19 with moderate to severe acute respiratory distress syndrome (ARDS) that required non-invasive ventilation and evidence of hyperinflammation (CRP \geq 100 mg/L and/or ferritin \geq 900 ng/mL). High-dose intravenous anakinra 5 mg/kg twice daily was administered for a median of 9 days, followed by SQ administration of anakinra 100 mg twice daily for 3 days to avoid inflammatory relapses. Patients in both the anakinra and control groups received hydroxychloroquine and lopinavir/ritonavir. In the anakinra group, reductions in CRP levels were noted over several days following anakinra initiation, and the 21-day survival rate was higher than in the control group (90% vs. 56%, respectively; $P = 0.009$). However, the patients in the anakinra group were younger than those in the control group (median age 62 years vs. 70 years, respectively), and fewer patients in the anakinra group had chronic kidney disease. High-dose anakinra was discontinued in seven patients (24%) because of adverse events (four patients developed bacteremia and three patients had elevated liver enzymes); however, retrospective assessment showed that these events occurred with similar frequency in the control group. An additional group of seven patients received low-dose SQ anakinra 100 mg twice daily; however, treatment in this group was stopped after 7 days because of lack of clinical or anti-inflammatory effects.⁵
- Other small case series have reported anakinra use for the treatment of COVID-19 and anecdotal evidence of improvement in outcomes.⁶

Clinical Trials

See [ClinicalTrials.gov](https://clinicaltrials.gov) for a list of clinical trials evaluating anakinra for the treatment of COVID-19.

Adverse Effects

Anakinra was not associated with any significant safety concerns when used in clinical trials for the treatment of sepsis.⁷⁻⁹ Increased rates of infection were reported with prolonged anakinra use in combination with tumor necrosis factor-alpha blockade, but not with short-term use.¹⁰

Considerations in Pregnancy

There is limited evidence on which to base a recommendation in pregnancy, but unintentional first trimester exposure is unlikely to be harmful.¹¹

Considerations in Children

Anakinra has been used extensively in the treatment of severely ill children with complications of rheumatologic conditions, including MAS. Pediatric data on the use of anakinra in ARDS/sepsis are limited.

Drug Availability

Procuring anakinra may be a challenge at some hospitals in the United States. Anakinra is FDA-approved only for SQ injection.

References

1. Anakinra (kineret) [package insert]. Food and Drug Administration. 2012. Available at:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103950s5136lbl.pdf. Accessed April 8, 2020.

2. Shakoory B, Carcillo JA, Chatham WW, et al. Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of macrophage activation syndrome: reanalysis of a prior Phase III trial. *Crit Care Med*. 2016;44(2):275-281. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26584195>.
3. Monteagudo LA, Boothby A, Gertner E. Continuous intravenous anakinra infusion to calm the cytokine storm in macrophage activation syndrome. *ACR Open Rheumatol*. 2020;2(5):276-282. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32267081>.
4. Huet T, Beaussier H, Voisin O, et al. Anakinra for severe forms of COVID-19: a cohort study. *Lancet Rheumatology*. 2020;2(7):e393-e400. Available at: [https://www.theLancet.com/pdfs/journals/lanrhe/PIIS2665-9913\(20\)30164-8.pdf](https://www.theLancet.com/pdfs/journals/lanrhe/PIIS2665-9913(20)30164-8.pdf).
5. Cavalli G, De Luca G, Campochiaro C, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *Lancet Rheumatology*. 2020;2(6): e325-e331. Available at: [https://www.theLancet.com/journals/lanrhe/article/PIIS2665-9913\(20\)30127-2/fulltext](https://www.theLancet.com/journals/lanrhe/article/PIIS2665-9913(20)30127-2/fulltext).
6. Aouba A, Baldolli A, Geffray L, et al. Targeting the inflammatory cascade with anakinra in moderate to severe COVID-19 pneumonia: case series. *Ann Rheum Dis*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32376597>.
7. Fisher CJ, Jr., Dhainaut JF, Opal SM, et al. Recombinant human interleukin 1 receptor antagonist in the treatment of patients with sepsis syndrome. Results from a randomized, double-blind, placebo-controlled trial. Phase III rhIL-1ra Sepsis Syndrome Study Group. *JAMA*. 1994;271(23):1836-1843. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8196140>.
8. Fisher CJ, Jr., Slotman GJ, Opal SM, et al. Initial evaluation of human recombinant interleukin-1 receptor antagonist in the treatment of sepsis syndrome: a randomized, open-label, placebo-controlled multicenter trial. *Crit Care Med*. 1994;22(1):12-21. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8124953>.
9. Opal SM, Fisher CJ, Jr., Dhainaut JF, et al. Confirmatory interleukin-1 receptor antagonist trial in severe sepsis: a Phase III, randomized, double-blind, placebo-controlled, multicenter trial. The Interleukin-1 Receptor Antagonist Sepsis Investigator Group. *Crit Care Med*. 1997;25(7):1115-1124. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9233735>.
10. Winthrop KL, Mariette X, Silva JT, et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) consensus document on the safety of targeted and biological therapies: an infectious diseases perspective (soluble immune effector molecules [II]: agents targeting interleukins, immunoglobulins and complement factors). *Clin Microbiol Infect*. 2018;24 Suppl 2:S21-S40. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29447987>.
11. Flint J, Panchal S, Hurrell A, et al. BSR and BHRP guideline on prescribing drugs in pregnancy and breastfeeding-Part II: analgesics and other drugs used in rheumatology practice. *Rheumatology (Oxford)*. 2016;55(9):1698-1702. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26750125>.

Interleukin-6 Inhibitors

Last Updated: August 27, 2020

Interleukin (IL)-6 is a pleiotropic, pro-inflammatory cytokine produced by a variety of cell types, including lymphocytes, monocytes, and fibroblasts. Infection by the severe acute respiratory syndrome-associated coronavirus (SARS-CoV) induces a dose-dependent production of IL-6 from bronchial epithelial cells.¹ COVID-19-associated systemic inflammation and hypoxic respiratory failure can be associated with heightened cytokine release, as indicated by elevated blood levels of IL-6, C-reactive protein (CRP), D-dimer, and ferritin.²⁻⁴ It is hypothesized that modulating the levels of IL-6 or its effects may alter the course of disease.

There are two classes of Food and Drug Administration (FDA)-approved IL-6 inhibitors: anti-IL-6 receptor monoclonal antibodies (e.g., sarilumab, tocilizumab) and anti-IL-6 monoclonal antibodies (siltuximab). These classes of drugs have been evaluated for the management of patients with COVID-19 who have systemic inflammation. The COVID-19 Treatment Guidelines Panel's (the Panel's) recommendations and clinical data to date are described below.

Recommendation

- The Panel **recommends against** the use of anti-IL-6 receptor monoclonal antibodies (e.g., **sarilumab, tocilizumab**) or anti-IL-6 monoclonal antibody (**siltuximab**) for the treatment of COVID-19, except in a clinical trial (**BI**).

Rationale

Preliminary, unpublished data from randomized, controlled trials failed to demonstrate efficacy of sarilumab or tocilizumab in patients with COVID-19. There are only limited, unpublished data describing the efficacy of siltuximab in patients with COVID-19.¹¹

Anti-Interleukin-6 Receptor Monoclonal Antibodies

Sarilumab

Sarilumab is a recombinant humanized anti-IL-6 receptor monoclonal antibody that is approved by the FDA for use in patients with rheumatoid arthritis. It is available as a subcutaneous (SQ) formulation and is not approved for the treatment of cytokine release syndrome (CRS). A placebo-controlled clinical trial is evaluating the use of an intravenous (IV) formulation of sarilumab administered as a single dose for COVID-19.

Clinical Data for COVID-19

Press Release: July 2, 2020: The efficacy and safety of sarilumab 400 mg IV and sarilumab 200 mg IV versus placebo was evaluated in patients hospitalized with COVID-19 in an adaptive Phase 2 and 3, randomized (2:2:1), double-blind, placebo-controlled trial (*ClinicalTrials.gov* Identifier [NCT04315298](https://clinicaltrials.gov/ct2/show/study/NCT04315298)). Randomization was stratified by severity of illness (i.e., severe, critical, multisystem organ dysfunction) and use of systemic corticosteroids for COVID-19. The Phase 2 component of the trial verified that sarilumab (at either dose) reduced CRP levels. The primary outcome for Phase 3 of the trial was change on a seven-point ordinal scale, and this phase was modified to focus on the dose of sarilumab 400 mg among the patients in the critically ill group. During the conduct of the trial, there were numerous amendments that increased the sample size and modified the dosing strategies being studied, and multiple interim analyses were performed. Ultimately, the trial findings to date do not support a clinical benefit of sarilumab for any of the disease severity subgroups or dosing strategies studied. Additional

detail (as would be included in a published manuscript) is required to fully evaluate the implications of these study findings.⁵

Adverse Effects

The primary lab abnormalities that have been reported with sarilumab treatment are transient and/or reversible elevations in liver enzymes that appear to be dose dependent and rare occurrences of neutropenia and thrombocytopenia. Risk for serious infections (e.g., tuberculosis [TB], bacterial or fungal infections) and bowel perforation have been reported only with long-term use of sarilumab.

Considerations in Pregnancy

There are insufficient data to determine whether there is a drug-associated risk for major birth defects or miscarriage. Monoclonal antibodies are actively transported across the placenta as pregnancy progresses (with greatest transfer during the third trimester) and may affect immune responses *in utero* in the exposed fetus.

Drug Availability

The SQ formulation of sarilumab is not approved for the treatment of CRS. The IV formulation is not approved by the FDA, but it is being studied in a clinical trial of hospitalized patients with COVID-19. A list of current clinical trials is available at [ClinicalTrials.gov](https://clinicaltrials.gov).

Tocilizumab

Tocilizumab is a recombinant humanized anti-IL-6 receptor monoclonal antibody that is approved by the FDA for use in patients with rheumatologic disorders and CRS induced by chimeric antigen receptor T cell (CAR-T) therapy. Tocilizumab can be dosed for IV or SQ injection. For CRS, the IV formulation should be used.⁶

Clinical Data for COVID-19

Press Release: July 29, 2020: In the industry-sponsored Phase 3 COVACTA trial ([ClinicalTrials.gov](https://clinicaltrials.gov) Identifier [NCT04320615](https://clinicaltrials.gov/ct2/show/study/NCT04320615)), 450 adults hospitalized with severe COVID-19-related pneumonia were randomized to receive tocilizumab or placebo. The trial failed to meet its primary endpoint or several key secondary endpoints. The primary outcome was improved clinical status, which was measured using a seven-point ordinal scale to assess clinical status based on the need for intensive care and/or ventilator use and the requirement for supplemental oxygen over a 4-week period. Key secondary outcomes included 4-week mortality. Differences in the primary outcome between the tocilizumab and placebo groups were not statistically significant (OR 1.19; 95% CI, 0.81–1.76; $P = 0.36$). At Week 4, mortality rates did not differ between the tocilizumab and placebo groups (19.7% vs. 19.4%; difference of 0.3%; 95% CI, -7.6% to 8.2%; $P = 0.94$). The difference in median number of ventilator-free days between the tocilizumab and placebo groups did not reach statistical significance (22 days for tocilizumab group vs. 16.5 days for placebo group; difference of 5.5 days; 95% CI, -2.8 to 13.0 days; $P = 0.32$). Infection rates at Week 4 were 38.3% in the tocilizumab group and 40.6% in the placebo group; serious infection rates were 21.0% and 25.9% in the tocilizumab and placebo groups, respectively.⁷

Published Study

Sixty-three adult patients hospitalized with COVID-19 were enrolled in a prospective, open-label study of tocilizumab for severe COVID-19. Criteria for inclusion in the study were polymerase chain reaction-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection; pulmonary involvement, assessed either by oxygen saturation (SaO_2) <93% on room air or $\text{PaO}_2/\text{FiO}_2$ ratio <300 mm Hg; and at least three of the following:

- CRP >10 times normal values,
- Ferritin >1,000 ng/mL,
- D-dimer >10 times normal values, *or*
- Lactate dehydrogenase >2 times the upper limit of normal.

The patients' mean age was 62.6 years and most of the patients (88%) were male; 39.7% of the patients were febrile, and 95.7% had bilateral pulmonary infiltrates. Five patients were on mechanical ventilation at baseline. All patients received off-label antiretroviral protease inhibitors. Patients received either tocilizumab (8 mg/kg) IV or tocilizumab (324 mg) SQ; within 24 hours after this initial dose of tocilizumab, a second dose was administered to 52 of the 63 patients. Following administration of tocilizumab, fevers resolved in all but one patient, and CRP, ferritin, and D-dimer levels declined. The mean PaO₂/FiO₂ ratio of the patients increased between admission (152 +/- 53 mm Hg) and Day 7 of hospitalization (284 +/- 116 mm Hg). No moderate or severe adverse events attributable to tocilizumab were reported. The overall mortality rate was 11% (7 of 63 patients). No details were provided regarding the rate of secondary infections after tocilizumab use. The authors report an association between earlier use of tocilizumab and reduced mortality; however, interpretation of this result is limited because the study results did not describe a comparison group or specify an a priori comparison.⁸

Clinical Trials

See [ClinicalTrials.gov](https://clinicaltrials.gov) for ongoing trials that are evaluating the use of tocilizumab for the treatment of COVID-19.

Adverse Effects

The primary laboratory abnormalities reported with tocilizumab treatment are elevated liver enzyme levels that appear to be dose dependent. Neutropenia or thrombocytopenia are uncommon. Additional adverse effects, such as risk for serious infections (e.g., TB, bacterial or fungal infections) and bowel perforation, have been reported only in the context of continuous dosing of tocilizumab.

Considerations in Pregnancy

There are insufficient data to determine whether there is a drug-associated risk for major birth defects or miscarriage. Monoclonal antibodies are actively transported across the placenta as pregnancy progresses (with greatest transfer during the third trimester) and may affect immune responses *in utero* in the exposed fetus.

Considerations in Children

In children, tocilizumab is frequently used for CRS following CAR-T therapy⁹ and it is occasionally used for macrophage activation syndrome.¹⁰ Pediatric data for its use in acute respiratory distress syndrome/sepsis are limited.

Drug Availability

Procuring IV tocilizumab may be a challenge at some hospitals in the United States.

Anti-Interleukin-6 Monoclonal Antibody

Siltuximab

Siltuximab is a recombinant human-mouse chimeric monoclonal antibody that binds IL-6 and is approved by the FDA for use in patients with Castleman's disease. Siltuximab prevents the binding of IL-6 to both soluble and membrane-bound IL-6 receptors, inhibiting IL-6 signaling. Siltuximab is dosed as an IV infusion.

Clinical Data in COVID-19

There are limited, unpublished data describing the efficacy of siltuximab in patients with COVID-19.¹¹ There are no data describing clinical experiences using siltuximab for patients with other novel coronavirus infections (i.e., severe acute respiratory syndrome [SARS], Middle East respiratory syndrome [MERS]).

Clinical Trials

See [ClinicalTrials.gov](https://www.clinicaltrials.gov) for a list of current clinical trials for siltuximab and COVID-19.

Adverse Effects

The primary adverse effects reported for siltuximab have been related to rash. Additional adverse effects (e.g., serious bacterial infections) have been reported only with long-term dosing of siltuximab once every 3 weeks.

Considerations in Pregnancy

There are insufficient data to determine whether there is a drug-associated risk for major birth defects or miscarriage. Monoclonal antibodies are transported across the placenta as pregnancy progresses (with greatest transfer during the third trimester) and may affect immune responses in utero in the exposed fetus.

Drug Availability

Procuring siltuximab may be a challenge at some hospitals in the United States.

References

1. Yoshikawa T, Hill T, Li K, Peters CJ, Tseng CT. Severe acute respiratory syndrome (SARS) coronavirus-induced lung epithelial cytokines exacerbate SARS pathogenesis by modulating intrinsic functions of monocyte-derived macrophages and dendritic cells. *J Virol*. 2009;83(7):3039-3048. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19004938>.
2. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32171076>.
3. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31986264>.
4. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China. *Clin Infect Dis*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32176772>.
5. Sanofi. Sanofi and Regeneron provide update on Kevzara® (sarilumab) Phase 3 U.S. trial in COVID-19 patients. 2020. Available at: <https://www.sanofi.com/en/media-room/press-releases/2020/2020-07-02-22-30-00>. Accessed August 10, 2020.
6. Le RQ, Li L, Yuan W, et al. FDA approval summary: tocilizumab for treatment of chimeric antigen receptor T cell-induced severe or life-threatening cytokine release syndrome. *Oncologist*. 2018;23(8):943-947. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29622697>.
7. Roche. Roche provides an update on the Phase III COVACTA trial of Actemra/RoActemra in hospitalised patients with severe COVID-19 associated pneumonia. 2020. Available at: <https://www.roche.com/investors/updates/inv-update-2020-07-29.htm>. Accessed August 10, 2020.
8. Sciascia S, Apra F, Baffa A, et al. Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in patients with severe COVID-19. *Clin Exp Rheumatol*. 2020;38(3):529-532. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32359035>.
9. Gardner RA, Ceppi F, Rivers J, et al. Preemptive mitigation of CD19 CAR T-cell cytokine release syndrome

without attenuation of antileukemic efficacy. *Blood*. 2019;134(24):2149-2158. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31697826>.

10. Yokota S, Itoh Y, Morio T, Sumitomo N, Daimaru K, Minota S. Macrophage activation syndrome in patients with systemic juvenile idiopathic arthritis under treatment with tocilizumab. *J Rheumatol*. 2015;42(4):712-722. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25684767>.
11. Gritti G, Raimondi F, Ripamonti D, et al. Use of siltuximab in patients with COVID-19 pneumonia requiring ventilatory support. *medRxiv*. 2020. Available at: <https://www.medrxiv.org/content/10.1101/2020.04.01.20048561v1>.

Kinase Inhibitors: Baricitinib and Other Janus Kinase Inhibitors, and Bruton's Tyrosine Kinase Inhibitors

Last Updated: February 11, 2021

Janus Kinase Inhibitors

The kinase inhibitors are proposed as treatments for COVID-19 because they can prevent phosphorylation of key proteins involved in the signal transduction that leads to immune activation and inflammation (e.g., the cellular response to proinflammatory cytokines such as interleukin [IL]-6).¹ Janus kinase (JAK) inhibitors interfere with phosphorylation of signal transducer and activator of transcription (STAT) proteins^{2,3} that are involved in vital cellular functions, including signaling, growth, and survival.

Immunosuppression induced by this class of drugs could potentially reduce the inflammation and associated immunopathologies observed in patients with COVID-19. Additionally, JAK inhibitors, particularly baricitinib, have theoretical direct antiviral activity through interference with viral endocytosis, potentially preventing entry into and infection of susceptible cells.⁴

Recommendations

- There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of baricitinib in combination with remdesivir for the treatment of COVID-19 in hospitalized patients, when corticosteroids can be used.
- In the rare circumstance when corticosteroids cannot be used, the Panel recommends **baricitinib** in combination with **remdesivir** for the treatment of COVID-19 in hospitalized, non-intubated patients who require oxygen supplementation (**BIIa**).
- The Panel **recommends against** the use of **baricitinib without remdesivir**, except in a clinical trial (**AIII**).
- There are insufficient data for the Panel to recommend either for or against the use of baricitinib in combination with corticosteroids for the treatment of COVID-19. Because both baricitinib and corticosteroids are potent immunosuppressants, there is potential for an additive risk of infection.
- The Panel **recommends against** the use of **JAK inhibitors other than baricitinib** for the treatment of COVID-19, except in a clinical trial (**AIII**).

Rationale

The Panel's recommendations for the use of baricitinib are based on data from the Adaptive COVID-19 Treatment Trial 2 (ACTT-2), a multinational, randomized, placebo-controlled trial of baricitinib use in hospitalized patients with COVID-19 pneumonia (see below for a full description of the ACTT-2 data for baricitinib). Participants (n = 1,033) were randomized 1:1 to oral baricitinib 4 mg or placebo, for up to 14 days, in combination with intravenous (IV) remdesivir, for up to 10 days. Participants who received baricitinib had a shorter time to clinical recovery than those who received placebo (median recovery time of 7 vs. 8 days, respectively). This treatment effect was most pronounced among those who required high-flow oxygen or non-invasive ventilation but were not on invasive mechanical ventilation. The difference in mortality between the treatment groups was not statistically significant.⁵

Corticosteroids have established efficacy in the treatment of severe and critical COVID-19 pneumonia (see the [Therapeutic Management](#) and [Corticosteroids](#) sections). The Panel's recommendations for the use of baricitinib are based on data for the benefit of corticosteroids and the uncertain clinical impact of

the modest difference in time to recovery between the placebo-treated and baricitinib-treated patients in the ACTT-2 trial. The Panel also considered the infrequent use of corticosteroids in the ACTT-2 trial, given that patients receiving corticosteroids for the treatment of COVID-19 at study entry were excluded.

On November 19, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for the use of baricitinib in combination with remdesivir in hospitalized adults and children aged ≥ 2 years with COVID-19 who require supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).⁶

The issuance of an EUA does not constitute FDA approval. An EUA indicates that a product may be effective in treating a serious or life-threatening disease or condition. FDA approval occurs when a product has been determined to provide benefits that outweigh its known and potential risks for the intended population.

Monitoring, Adverse Effects, and Drug-Drug Interactions

Most of the data on adverse effects of JAK inhibitors refer to chronic use of the agents. Adverse effects include infections (typically respiratory and urinary tract infections) and the reactivation of herpes viruses. Additional toxicities include myelosuppression and transaminase elevations. In addition, there may be a slightly higher risk of thrombotic events and gastrointestinal perforation in patients who receive JAK inhibitors.

Complete blood count with differential, liver function tests, and kidney function tests should be obtained in all patients before baricitinib is administered and during treatment as clinically indicated. Screening for viral hepatitis and tuberculosis should be considered. Considering its immunosuppressive effects, all patients receiving baricitinib should also be monitored for new infections.

The ACTT-2 study evaluated oral baricitinib 4 mg once daily;⁵ however, the standard dosage of baricitinib for FDA-approved indications is 2 mg once daily. Baricitinib use is not recommended in patients with impaired hepatic or renal function (estimated GFR < 60 mL/min/1.73 m²).⁷ There are limited clinical data on the use of baricitinib in combination with strong organic anion transporter 3 inhibitors, and, in general, coadministration is not advised.^{7,8}

Considerations in Pregnancy

There is a paucity of data on the use of JAK inhibitors in pregnancy. As small molecule-drugs, JAK inhibitors are likely to pass through the placenta, and therefore fetal risk cannot be ruled out.⁹ Decisions about the administration of JAK inhibitors must include shared decision-making with the pregnant individual, considering potential maternal benefit and fetal risks. Factors that may weigh into the decision-making process include maternal COVID-19 severity, comorbidities, and gestational age. When the benefits outweigh the risks, use of JAK inhibitors may be considered.

Considerations in Children

An EUA has been issued for the use of baricitinib in combination with remdesivir in hospitalized adults and children aged ≥ 2 years with COVID-19 who require supplemental oxygen, invasive mechanical ventilation, or ECMO. The safety and efficacy of baricitinib or other JAK inhibitors has not been evaluated in pediatric patients with COVID-19, and data on the use of the drugs in children with other conditions are extremely limited. Thus, there are insufficient data to recommend either for or against the use of baricitinib in combination with remdesivir for the treatment of COVID-19 in hospitalized children when corticosteroids cannot be used. Use of JAK inhibitors other than baricitinib for the treatment of COVID-19 in pediatric patients is not recommended, except in a clinical trial.

Baricitinib

Baricitinib is an oral JAK inhibitor that is selective for JAK1 and JAK2 and FDA approved for the treatment of rheumatoid arthritis.⁷ Baricitinib can modulate downstream inflammatory responses via JAK1/JAK2 inhibition and has exhibited dose-dependent inhibition of IL-6-induced STAT3 phosphorylation.¹⁰ Baricitinib has postulated antiviral effects by blocking severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from entering and infecting lung cells.¹¹ Baricitinib reduced inflammation and lung pathology in macaques infected with SARS-CoV-2 but an antiviral effect was not confirmed.¹²

Clinical Data for COVID-19

The multicenter, randomized, double-blind ACTT-2 trial compared (1:1 allocation) oral baricitinib 4 mg daily (for up to 14 days or until hospital discharge) versus placebo, both given in combination with IV remdesivir (for 10 days or until hospital discharge). The trial included 1,033 patients hospitalized with moderate to severe COVID-19. The primary endpoint was time to recovery, which was defined as reaching Category 1 (not hospitalized, no limitations), Category 2 (not hospitalized, with limitations), or Category 3 (hospitalized, no active medical problems) on an eight-category ordinal scale within 28 days of treatment initiation. Patients who were using a medication off-label as a specific treatment for COVID-19, including corticosteroids, at study entry were excluded from the trial. In the overall cohort, the median time to recovery was shorter in the baricitinib plus remdesivir arm (7 days) than in the placebo plus remdesivir arm (8 days) (rate ratio for recovery 1.16; 95% CI, 1.01–1.32; $P = 0.03$). In subgroup analyses according to disease severity, the difference in time to recovery was greatest among the participants who required high-flow oxygen or non-invasive ventilation (10 vs. 18 days for the baricitinib and placebo recipients, respectively; rate ratio for recovery 1.51; 95% CI, 1.10–2.08). However, the treatment effect within this subgroup should be interpreted with caution given the relatively small sample size. Within the subgroup of patients on invasive mechanical ventilation or ECMO at study entry, it was not possible to estimate the median time to recovery within the first 28 days following treatment initiation, and there was no evidence of benefit with baricitinib use (rate ratio for recovery 1.08; 95% CI, 0.59–1.97). Improvement across ordinal categories at Day 15 was a key secondary endpoint, and again baricitinib demonstrated a significant benefit only in the subgroup of patients requiring high-flow oxygen or non-invasive ventilation (OR 2.3; 95% CI, 1.4–3.7). Mortality by 28 days was lower in the baricitinib arm than in the placebo arm, but the difference was not statistically significant (OR 0.65; 95% CI, 0.39–1.09). There was no evidence that the risk of serious adverse events or new infections was higher in the baricitinib arm than in the placebo arm (16% vs. 20% for adverse events and 6% vs. 11% for new infections in the baricitinib and placebo arms, respectively).⁵

Even though the use of corticosteroids for the treatment of COVID-19 was prohibited at study entry, the protocol allowed for the adjunctive use of corticosteroids at the discretion of the treating provider for the treatment of standard medical indications (e.g., asthma exacerbation, acute respiratory distress syndrome, chronic obstructive pulmonary disease). During the study, 10.9% of the patients in the baricitinib group and 12.9% in the placebo group were prescribed corticosteroids. Overall, the incidence of serious or non-serious infections was lower in the baricitinib group (30 patients [6%]) than in the placebo group (57 patients [11%]) (RD -5; 95% CI, -9 to -2). There were no statistically significant differences between the baricitinib and placebo arms in the frequency of pulmonary embolism (5 vs. 2 patients, respectively) or deep vein thrombosis (11 vs. 9 patients, respectively).

Preliminary results of this study suggest that baricitinib improves time to recovery in patients who require supplemental oxygen but not invasive mechanical ventilation. However, a key limitation of the study is the inability to evaluate the treatment effect of baricitinib in addition to, or in comparison to, corticosteroids used as standard treatment for severe or critical COVID-19 pneumonia.

Clinical Trials

Please check [ClinicalTrials.gov](https://clinicaltrials.gov) for the latest information on studies of baricitinib and COVID-19.

Ruxolitinib

Ruxolitinib is an oral JAK inhibitor selective for JAK1 and JAK2 that is currently approved for myelofibrosis, polycythemia vera, and acute graft-versus-host disease.¹³ Like baricitinib, it can modulate downstream inflammatory responses via JAK1/JAK2 inhibition and has exhibited dose-dependent inhibition of IL-6-induced STAT3 phosphorylation.¹⁰ Ruxolitinib also has postulated antiviral effects by blocking SARS-CoV-2 from entering and infecting lung cells.¹¹

Clinical Data for COVID-19

A small, single-blind, randomized, controlled Phase 2 trial in patients with COVID-19 in China compared ruxolitinib 5 mg orally twice daily (n = 20) with placebo (administered as vitamin C 100 mg; n = 21), both given in combination with SOC therapy. The median age of the patients was 63 years. There were no significant demographic differences between the two arms. Treatment with ruxolitinib was associated with a nonsignificant reduction in the median time to clinical improvement (12 days for ruxolitinib vs. 15 days for placebo; $P = 0.15$), defined as a two-point improvement on a seven-category ordinal scale or as hospital discharge. There was no difference between the groups in the median time to discharge (17 days for ruxolitinib vs. 16 days for placebo; $P = 0.94$). More patients in the ruxolitinib group than in the placebo group had radiographic improvement on computed tomography scans of the chest at Day 14 (90% for ruxolitinib vs. 61.9% for placebo; $P = 0.05$) and a shorter time to recovery from initial lymphopenia (5 days for ruxolitinib vs. 8 days for placebo; $P = 0.03$), when it was present. The use of ruxolitinib was not associated with an increased risk of adverse events or mortality (no deaths in the ruxolitinib arm vs. three deaths [14% of patients] in the control arm). Despite the theoretical antiviral properties of JAK inhibitors, there was no significant difference in the time to viral clearance among the patients who had detectable viral loads at the time of randomization to ruxolitinib treatment (n = 8) or placebo (n = 9). Limitations of this study include the small sample size, the exclusion of ventilated patients at study entry, and the concomitant use of antivirals and steroids by 70% of the patients.¹⁴

Clinical Trials

Please check [ClinicalTrials.gov](https://clinicaltrials.gov) for the latest information on studies of ruxolitinib and COVID-19.

Tofacitinib

Tofacitinib is the prototypical JAK inhibitor, predominantly selective for JAK1 and JAK3, with modest activity against JAK2, and, as such, can block signaling from gamma-chain cytokines (e.g., IL-2, IL-4) and gp 130 proteins (e.g., IL-6, IL-11, interferons). It is an oral agent first approved by the FDA for the treatment of rheumatoid arthritis and has been shown to decrease levels of IL-6 in patients with this disease.¹⁵ Tofacitinib is also FDA approved for the treatment of psoriatic arthritis, juvenile idiopathic arthritis, and ulcerative colitis.¹⁶

Clinical Data for COVID-19

There are no clinical data on the use of tofacitinib to treat COVID-19.

Considerations in Pregnancy

Pregnancy registries provide some outcome data on tofacitinib used during pregnancy for other conditions (e.g., ulcerative colitis, rheumatoid arthritis, psoriasis). Among the 33 cases reported, pregnancy outcomes were similar to those among the general pregnant population.¹⁷⁻¹⁹

Clinical Trials

Please check [ClinicalTrials.gov](https://clinicaltrials.gov) for the latest information on studies of tofacitinib and COVID-19.

Bruton's Tyrosine Kinase Inhibitors

Bruton's tyrosine kinase (BTK) is a signaling molecule of the B-cell antigen receptor and cytokine receptor pathways.

Recommendation

- The Panel **recommends against** the use of **BTK inhibitors** for the treatment of COVID-19, except in a clinical trial (**AIII**).

Acalabrutinib

Acalabrutinib is a second-generation, oral BTK inhibitor that is FDA approved to treat B-cell malignancies (i.e., chronic lymphocytic leukemia/small lymphocytic lymphoma, mantle cell lymphoma). It has a better toxicity profile than first-generation BTK inhibitors (e.g., ibrutinib) because of less off-target activity for other kinases.²⁰ Acalabrutinib is proposed for use in patients with COVID-19 because it can modulate signaling that promotes inflammation.

Clinical Data for COVID-19

Data regarding acalabrutinib are limited to the results from a retrospective case series of 19 patients with severe COVID-19.²¹ Evaluation of the data to discern any clinical benefit is limited by the study's small sample size and lack of a control group.

Clinical Trials

Please check [ClinicalTrials.gov](https://clinicaltrials.gov) for the latest information on studies of acalabrutinib and COVID-19.

Ibrutinib

Ibrutinib is a first-generation BTK inhibitor that is FDA approved to treat various B-cell malignancies²² and to prevent chronic graft-versus-host disease in stem cell transplant recipients.²³ Based on results from a small case series, ibrutinib has been theorized to reduce inflammation and protect against ensuing lung injury in patients with COVID-19.²⁴

Clinical Data for COVID-19

Data regarding ibrutinib are limited to those from an uncontrolled, retrospective case series of six patients with COVID-19 who were receiving the drug for a condition other than COVID-19.²⁴ Evaluation of the data for any clinical benefit is limited by the series' small sample size and lack of a control group.

Clinical Trials

Please check [ClinicalTrials.gov](https://clinicaltrials.gov) for the latest information on studies of ibrutinib and COVID-19.

Zanubrutinib

Zanubrutinib is a second-generation, oral BTK inhibitor that is FDA approved to treat mantle cell lymphoma.²⁵ It has been shown to have fewer toxicities than first-generation BTK inhibitors (e.g., ibrutinib) because of less off-target activity for other kinases.²⁶ Zanubrutinib is proposed to benefit patients with COVID-19 by modulating signaling that promotes inflammation.

Clinical Data for COVID-19

There are no clinical data on the use of zanubrutinib to treat COVID-19.

Clinical Trials

Please check [ClinicalTrials.gov](https://clinicaltrials.gov) for the latest information on studies of zanubrutinib and COVID-19.

Adverse Effects and Monitoring

Hemorrhage and cardiac arrhythmia have occurred in patients who received BTK inhibitors.

Considerations in Pregnancy

There is a paucity of data on human pregnancy and BTK inhibitor use. In animal studies, acalabrutinib and ibrutinib in doses exceeding the therapeutic human dose were associated with interference with embryofetal development.^{22,27} Based on these data, use of BTK inhibitors that occurs during organogenesis may be associated with fetal malformations. The impact of use later in pregnancy is unknown. Risks of use should be balanced against potential benefits.

Considerations in Children

The safety and efficacy of BTK inhibitors have not been evaluated in pediatric patients with COVID-19, and data on the use of the drugs in children with other conditions are extremely limited. Use of BTK inhibitors for the treatment of COVID-19 in pediatric patients is **not recommended**, except in a clinical trial.

References

1. Zhang W, Zhao Y, Zhang F, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): the perspectives of clinical immunologists from China. *Clin Immunol*. 2020;214:108393. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32222466>.
2. Babon JJ, Lucet IS, Murphy JM, Nicola NA, Varghese LN. The molecular regulation of Janus kinase (JAK) activation. *Biochem J*. 2014;462(1):1-13. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25057888>.
3. Bousoik E, Montazeri Aliabadi H. “Do we know jack” about JAK? A closer look at JAK/STAT signaling pathway. *Front Oncol*. 2018;8:287. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30109213>.
4. Stebbing J, Phelan A, Griffin I, et al. COVID-19: combining antiviral and anti-inflammatory treatments. *Lancet Infect Dis*. 2020;20(4):400-402. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32113509>.
5. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus remdesivir for hospitalized adults with COVID-19. *N Engl J Med*. 2020;Published online ahead of print. Available at: <https://pubmed.ncbi.nlm.nih.gov/33306283/>.
6. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of baricitinib. 2020. Available at: <https://www.fda.gov/media/143823/download>. Accessed December 11, 2020.
7. Baricitinib (Olumiant) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/207924s001lbl.pdf.
8. Posada MM, Cannady EA, Payne CD, et al. Prediction of transporter-mediated drug-drug interactions for baricitinib. *Clin Transl Sci*. 2017;10(6):509-519. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28749581>.
9. Sammaritano LR, Bermas BL, Chakravarty EE, et al. 2020 American College of Rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases. *Arthritis Rheumatol*. 2020;72(4):529-556. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32090480>.
10. McInnes IB, Byers NL, Higgs RE, et al. Comparison of baricitinib, upadacitinib, and tofacitinib mediated regulation of cytokine signaling in human leukocyte subpopulations. *Arthritis Res Ther*. 2019;21(1):183. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31375130>.

11. Richardson P, Griffin I, Tucker C, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Lancet*. 2020;395(10223):e30-e31. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32032529>.
12. Hoang TN, Pino M, Boddapati AK, et al. Baricitinib treatment resolves lower-airway macrophage inflammation and neutrophil recruitment in SARS-CoV-2-infected rhesus macaques. *Cell*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33278358>.
13. Ruxolitinib (JAKAFI) [package insert]. 2020. Available at: <https://www.jakafi.com/pdf/prescribing-information.pdf>. Accessed: May 28, 2020.
14. Cao Y, Wei J, Zou L, et al. Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): A multicenter, single-blind, randomized controlled trial. *J Allergy Clin Immunol*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32470486>.
15. Migita K, Izumi Y, Jiuchi Y, et al. Effects of Janus kinase inhibitor tofacitinib on circulating serum amyloid A and interleukin-6 during treatment for rheumatoid arthritis. *Clin Exp Immunol*. 2014;175(2):208-214. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24665995>.
16. Tofacitinib (Xeljanz) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/203214s024,208246s010lbl.pdf.
17. Clowse ME, Feldman SR, Isaacs JD, et al. Pregnancy outcomes in the tofacitinib safety databases for rheumatoid arthritis and psoriasis. *Drug Saf*. 2016;39(8):755-762. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27282428>.
18. Mahadevan U, Dubinsky MC, Su C, et al. Outcomes of pregnancies with maternal/paternal exposure in the tofacitinib safety databases for ulcerative colitis. *Inflamm Bowel Dis*. 2018;24(12):2494-2500. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29982686>.
19. Wieringa JW, van der Woude CJ. Effect of biologicals and JAK inhibitors during pregnancy on health-related outcomes in children of women with inflammatory bowel disease. *Best Pract Res Clin Gastroenterol*. 2020;44-45:101665. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32359679>.
20. Owen C, Berinstein NL, Christofides A, Sehn LH. Review of Bruton tyrosine kinase inhibitors for the treatment of relapsed or refractory mantle cell lymphoma. *Curr Oncol*. 2019;26(2):e233-e240. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31043832>.
21. Roschewski M, Lionakis MS, Sharman JP, et al. Inhibition of Bruton tyrosine kinase in patients with severe COVID-19. *Sci Immunol*. 2020;5(48). Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32503877>.
22. Ibrutinib (Imbruvica) [package insert]. Food and Drug Administration. 2015. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205552s002lbl.pdf.
23. Food and Drug Administration. FDA expands ibrutinib indications to chronic GVHD. 2017. Available at: <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-expands-ibrutinib-indications-chronic-gvhd>. Accessed February 1, 2021.
24. Treon SP, Castillo JJ, Skarbnik AP, et al. The BTK inhibitor ibrutinib may protect against pulmonary injury in COVID-19-infected patients. *Blood*. 2020;135(21):1912-1915. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32302379>.
25. Zanubrutinib (Brukinsa) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213217s000lbl.pdf.
26. Tam C, Grigg AP, Opat S, et al. The BTK inhibitor, Bgb-3111, is safe, tolerable, and highly active in patients with relapsed/refractory B-cell malignancies: initial report of a Phase 1 first-in-human trial. *Blood*. 2015;126(23):832. Available at: <https://ashpublications.org/blood/article/126/23/832/136525/The-BTK-Inhibitor-Bgb-3111-Is-Safe-Tolerable-and>.
27. Acalabrutinib (Calquence) [package insert]. Food and Drug Administration. 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/210259s000lbl.pdf.

Immunoglobulins: Non-SARS-CoV-2 Specific

Last Updated: July 17, 2020

Recommendation

- The COVID-19 Treatment Guidelines Panel **recommends against** the use of non-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-specific **intravenous immunoglobulin (IVIG)** for the treatment of COVID-19, except in a clinical trial (**AIII**). This recommendation **should not preclude** the use of IVIG when otherwise indicated for the treatment of complications that arise during the course of COVID-19.

Rationale for Recommendation

It is unknown whether products derived from the plasma of donors without confirmed SARS-CoV-2 infection contain high titer of SARS-CoV-2 neutralizing antibodies. Furthermore, although other blood components in IVIG may have general immunomodulatory effects, it is unclear whether these theoretical effects will benefit patients with COVID-19.

Clinical Data for COVID-19

This study has not been peer reviewed.

A retrospective, non-randomized cohort study of IVIG for the treatment of COVID-19 was conducted across eight treatment centers in China between December 2019 and March 2020. The study showed no difference in 28-day or 60-day mortality between 174 patients who received IVIG and 151 patients who did not receive IVIG.¹ More patients in the IVIG group had severe disease at study entry (71 patients [41%] with critical status in the IVIG group vs. 32 patients [21%] in the non-IVIG group). The median hospital stay was longer in the IVIG group (24 days) than in the non-IVIG group (16 days), and the median duration of disease was also longer (31 days in the IVIG group vs. 23 days in the non-IVIG group). A subgroup analysis that was limited to the critically ill patients suggested a mortality benefit at 28 days, which was no longer significant at 60 days.

The results of this study are difficult to interpret because of important limitations in the study design. In particular, patients were not randomized to receive either IVIG or no IVIG, and the patients in the IVIG group were older and more likely to have coronary heart disease than those in the non-IVIG group. In addition, the IVIG group had a higher proportion of patients with severe COVID-19 disease at study entry. Patients in both groups also received many concomitant therapies for COVID-19.

Considerations in Pregnancy

IVIG is commonly used in pregnancy for other indications such as immune thrombocytopenia with an acceptable safety profile.^{2,3}

Considerations in Children

IVIG has been widely used in children for the treatment of a number of conditions, including Kawasaki disease, and is generally safe.⁴ IVIG has been used in pediatric patients with COVID-19 and multiorgan inflammatory syndrome in children (MIS-C), especially those with a Kawasaki disease-like presentation, but the efficacy of IVIG in the management of MIS-C is still under investigation.

References

1. Shao Z, Feng Y, Zhong L, et al. Clinical efficacy of intravenous immunoglobulin therapy in critical patients with COVID-19: A multicenter retrospective cohort study. *medRxiv*. 2020;Preprint. Available at: <https://www.medrxiv.org/content/10.1101/2020.04.11.20061739v2>.
2. Committee on Practice Bulletins—Obstetrics. ACOG practice bulletin No. 207: thrombocytopenia in pregnancy. *Obstet Gynecol*. 2019;133(3):e181-e193. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30801473>.
3. Neunert C, Lim W, Crowther M, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood*. 2011;117(16):4190-4207. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21325604>.
4. Agarwal S, Agrawal DK. Kawasaki disease: etiopathogenesis and novel treatment strategies. *Expert Rev Clin Immunol*. 2017;13(3):247-258. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27590181>.

Table 4b. Characteristics of Immunomodulators Under Evaluation for the Treatment of COVID-19

Last Updated: February 11, 2021

- The information in this table is derived from data on the use of these drugs for FDA-approved indications or in investigational trials, and it is supplemented with data on their use in patients with COVID-19, when available.
- There are limited or no data on dose modifications for patients with organ failure or those who require extracorporeal devices. Please refer to product labels, when available.
- There are currently not enough data to determine whether certain medications can be safely coadministered with therapies for the treatment of COVID-19. When using concomitant medications with similar toxicity profiles, consider performing additional safety monitoring.
- The potential additive, antagonistic, or synergistic effects and the safety of using combination therapies for the treatment of COVID-19 are unknown. Clinicians are encouraged to report AEs to the [FDA Medwatch program](#).

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Corticosteroids					
Dexamethasone	Dose for COVID-19: <ul style="list-style-type: none"> • Dexamethasone 6 mg IV or PO once daily, for up to 10 days or until hospital discharge, whichever comes first¹ 	<ul style="list-style-type: none"> • Hyperglycemia • Secondary infections • Reactivation of latent infections (e.g., HBV, HSV, strongyloidiasis, TB) • Psychiatric disturbances • Avascular necrosis • Adrenal insufficiency • Increased blood pressure 	<ul style="list-style-type: none"> • Blood glucose • Blood pressure • Signs and symptoms of new infection • When initiating dexamethasone, consider appropriate screening and treatment to reduce the risk of <i>Strongyloides</i> hyperinfection in patients at high-risk of strongyloidiasis 	<ul style="list-style-type: none"> • Moderate CYP3A4 inducer • CYP3A4 substrate • Although coadministration of RDV and dexamethasone has not been formally studied, a clinically significant PK interaction is not predicted (Gilead, written communication, August 2020). 	<p>For the Panel's recommendations on the use of corticosteroids, please see Therapeutic Management of Patients With COVID-19.</p> <ul style="list-style-type: none"> • If dexamethasone is not available, an alternative corticosteroid such as prednisone, methylprednisolone, or hydrocortisone can be used. • The approximate total daily dose equivalencies for these glucocorticoids to

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Corticosteroids , continued					
Dexamethasone, continued		<ul style="list-style-type: none"> Peripheral edema Myopathy (particularly if used with neuromuscular blocking agents) When used during outbreaks of other novel coronavirus infections (i.e., MERS and SARS), corticosteroid therapy was associated with delayed virus clearance.^{2,3} 	(e.g., patients from tropical, subtropical, or warm temperate regions or who engage in agricultural activities) or fulminant reactivations of HBV. ⁴⁻⁶		<p>dexamethasone 6 mg (PO or IV) are: prednisone 40 mg, methylprednisolone 32 mg, and hydrocortisone 160 mg.</p> <ul style="list-style-type: none"> A list of clinical trials is available: Dexamethasone
Interferons					
Interferon Alfa	<p>PegIFN Alfa-2a Dose for MERS:</p> <ul style="list-style-type: none"> PegIFN alfa-2a 180 mcg SQ once weekly for 2 weeks^{7,8} <p>IFN Alfa-2b Dose for COVID-19 in Clinical Trials:</p> <ul style="list-style-type: none"> Nebulized IFN alfa-2b 5 million international units twice daily (no duration listed in the study methods)⁹ 	<ul style="list-style-type: none"> Flu-like symptoms (e.g., fever, fatigue, myalgia)¹⁰ Injection site reactions Liver function abnormalities Decreased blood counts Worsening depression Insomnia Irritability Nausea Vomiting Hypertension Induction of autoimmunity 	<ul style="list-style-type: none"> CBC with differential Liver enzymes; avoid if Child-Pugh Score >6 Depression, psychiatric symptoms Reduce dose in patients with CrCl <30 mL/min. 	<ul style="list-style-type: none"> Low potential for drug interactions Inhibition of CYP1A2 	<ul style="list-style-type: none"> The Panel recommends against the use of IFNs for the treatment of patients with severe and critical COVID-19, except in a clinical trial (AIII). For COVID-19, IFN alfa has primarily been used as nebulization and usually as part of a combination regimen. Neither nebulized IFN alfa-2b nor IFN alfa-1b are FDA-approved for use in the United States. Use with caution with other hepatotoxic agents.

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Interferons, continued					
Interferon Alfa, continued					<ul style="list-style-type: none"> • Reduce dose if ALT >5 times ULN; discontin-ue if bilirubin level also increases. • Reduce dose or discontinue if neutropenia or thrombocytopenia occur. • A list of clinical trials is available: Interferon
Interferon Beta	<p>IFN Beta-1a Dose for MERS:</p> <ul style="list-style-type: none"> • IFN beta-1a 44 mcg SQ 3 times weekly⁸ <p>Dose for COVID-19:</p> <ul style="list-style-type: none"> • Dose and duration unknown <p>IFN Beta-1b Dose for COVID-19:</p> <ul style="list-style-type: none"> • IFN beta-1b 8 million international units SQ every other day, up to 7 days total¹¹ 	<ul style="list-style-type: none"> • Flu-like symptoms (e.g., fever, fatigue, myalgia)¹² • Leukopenia, neutropenia, thrombocytopenia, lymphopenia • Liver function abnormalities (ALT > AST) • Injection site reactions • Headache • Hypertonia • Pain • Rash • Worsening depression • Induction of autoimmunity 	<ul style="list-style-type: none"> • Liver enzymes • CBC with differential • Worsening CHF • Depression, suicidal ideation 	<ul style="list-style-type: none"> • Low potential for drug interactions 	<ul style="list-style-type: none"> • The Panel recommends against the use of IFNs for the treatment of patients with severe or critical COVID-19, except in a clinical trial (AllI). • There are insufficient data to recommend either for or against the use of IFN beta for the treatment of early (i.e., <7 days from symptom onset) mild to moderate COVID-19. • Use with caution with other hepatotoxic agents. • Reduce dose if ALT >5 times ULN. • A list of clinical trials is available: Interferon <p>Availability:</p> <ul style="list-style-type: none"> • Several products are available in the United States; product doses differ.

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Interferons, continued					
Interferon Beta, continued					<i>IFN Beta-1a Products:</i> <ul style="list-style-type: none"> • Avonex, Rebif <i>IFN Beta-1b Products:</i> <ul style="list-style-type: none"> • Betaseron, Extavia
Interleukin-1 Inhibitor					
Anakinra	Dose for Rheumatoid Arthritis: <ul style="list-style-type: none"> • Anakinra 100 mg SQ once daily Dose for COVID-19: <ul style="list-style-type: none"> • Dose and duration vary by study • Has also been used as IV infusion 	<ul style="list-style-type: none"> • Neutropenia (particularly with concomitant use of other agents that can cause neutropenia) • Anaphylaxis • Headache • Nausea • Diarrhea • Sinusitis • Arthralgia • Flu-like symptoms • Abdominal pain • Injection site reactions • Liver enzyme elevations 	<ul style="list-style-type: none"> • CBC with differential • Renal function (reduce dose in patients with CrCl <30 mL/min) • Liver enzymes 	<ul style="list-style-type: none"> • Use with TNF-blocking agents is not recommended due to increased risk of infection 	<ul style="list-style-type: none"> • There are insufficient data for the Panel to recommend either for or against the use of IL-1 inhibitors (e.g., anakinra) for the treatment of COVID-19. • A list of clinical trials is available: Anakinra
Interleukin-6 Inhibitors					
<i>Anti-Interleukin-6 Receptor Monoclonal Antibodies</i>					
Sarilumab ¹³	Dose for COVID-19 in Clinical Trial (See ClinicalTrials.gov Identifier NCT04315298): <ul style="list-style-type: none"> • Sarilumab 400 mg IV (single dose)¹⁴ 	<ul style="list-style-type: none"> • Neutropenia, thrombocytopenia • Gastrointestinal perforation • HSR 	<ul style="list-style-type: none"> • Monitor for HSR • Monitor for infusion reactions • Neutrophils • Platelets 	<ul style="list-style-type: none"> • Elevated IL-6 may downregulate CYP enzymes; use of sarilumab may lead to increased metabolism of drugs that are 	<ul style="list-style-type: none"> • For patients who are within 24 hours of admission to the ICU and who require invasive or noninvasive mechanical ventilation or high-flow oxygen (>0.4 FiO₂/30 L/min of oxygen

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Interleukin-6 Inhibitors , continued					
<i>Anti-Interleukin-6 Receptor Monoclonal Antibodies</i> , continued					
Sarilumab ¹³	<ul style="list-style-type: none"> • REMAP-CAP evaluated sarilumab for IV administration, which is not the approved formulation in the United States. 	<ul style="list-style-type: none"> • Increased liver enzymes • HBV reactivation • Infusion reaction possible 	<ul style="list-style-type: none"> • Liver enzymes 	CYP450 substrates. <ul style="list-style-type: none"> • Effects on CYP450 may persist for weeks after therapy. 	flow), there are insufficient data to recommend either for or against the use of sarilumab for the treatment of COVID-19. <ul style="list-style-type: none"> • For patients who do not require ICU-level care or who are admitted to the ICU but do not meet the above criteria, the Panel recommends against the use of sarilumab for the treatment of COVID-19, except in a clinical trial (BIIa). • Treatment with sarilumab may mask signs of acute inflammation or infection (i.e., by suppressing fever and CRP levels). • A list of clinical trials is available: Sarilumab
Tocilizumab ¹⁵	Dose for COVID-19 in Clinical Trial: <ul style="list-style-type: none"> • Tocilizumab 8 mg/kg IV once • Dose should not exceed tocilizumab 800 mg. • If tocilizumab is used, administer with a course of dexamethasone therapy. 	<ul style="list-style-type: none"> • Infusion-related reactions • HSR • Gastrointestinal perforation • Hepatotoxicity • Treatment-related changes in neutrophils, platelets, lipids, and liver enzymes 	<ul style="list-style-type: none"> • Monitor for HSR • Monitor for infusion reactions • Neutrophils • Platelets • Liver enzymes 	<ul style="list-style-type: none"> • Elevated IL-6 may downregulate CYP enzymes; use of tocilizumab may lead to increased metabolism of drugs that are CYP450 substrates. • Effects on CYP450 may persist for weeks after therapy. 	<ul style="list-style-type: none"> • For patients who are within 24 hours of admission to the ICU and who require invasive or noninvasive mechanical ventilation or high-flow oxygen (>0.4 FiO₂/30 L/min of oxygen flow), there are insufficient data to recommend either for or against the use of tocilizumab for the treatment of COVID-19.

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Interleukin-6 Inhibitors , continued					
<i>Anti-Interleukin-6 Receptor Monoclonal Antibodies</i> , continued					
Tocilizumab ¹⁵ , continued		<ul style="list-style-type: none"> • HBV reactivation 			<ul style="list-style-type: none"> • Some Panel members would administer a single dose of tocilizumab (8 mg/kg actual body weight up to 800 mg) in addition to dexamethasone to patients who meet the above criteria and who are also exhibiting rapid progression of respiratory failure. • For patients who do not require ICU-level care or who are admitted to the ICU but do not meet the above criteria, the Panel recommends against the use of tocilizumab for the treatment of COVID-19, except in a clinical trial (BIIa). • May mask signs of acute inflammation or infection (i.e., by suppressing fever and CRP levels). • The SQ formulation of tocilizumab is not intended for IV administration. • A list of clinical trials is available: Tocilizumab

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Interleukin-6 Inhibitors , continued					
<i>Anti-Interleukin-6 Monoclonal Antibody</i>					
Siltuximab	Dose for Multicentric Castleman Disease: <ul style="list-style-type: none"> Siltuximab 11 mg/kg administered over 1 hour by IV infusion every 3 weeks¹⁶ Dose for COVID-19: <ul style="list-style-type: none"> Dose and duration unknown 	<ul style="list-style-type: none"> Infusion-related reaction HSR Gastrointestinal perforation Neutropenia Hypertension Dizziness Rash Pruritus Hyperuricemia 	<ul style="list-style-type: none"> Monitor for HSR Monitor for infusion reactions Neutrophils 	<ul style="list-style-type: none"> Elevated IL-6 may downregulate CYP enzymes; use of siltuximab may lead to increased metabolism of drugs that are CYP450 substrates. Effects on CYP450 may persist for weeks after therapy. 	<ul style="list-style-type: none"> The Panel recommends against the use of siltuximab for the treatment of COVID-19, except in a clinical trial (Alla). May mask signs of acute inflammation or infection (i.e., by suppressing fever and CRP levels). A list of clinical trials is available: Siltuximab
Kinase Inhibitors					
<i>Bruton's Tyrosine Kinase Inhibitors</i>					
Acalabrutinib	Dose for FDA-Approved Indications: <ul style="list-style-type: none"> Acalabrutinib 100 mg PO every 12 hours Dose for COVID-19: <ul style="list-style-type: none"> Dose and duration unknown 	<ul style="list-style-type: none"> Hemorrhage Cytopenias (neutropenia, anemia, thrombocytopenia, lymphopenia) Atrial fibrillation and flutter Infection Headache Diarrhea Fatigue Myalgia 	<ul style="list-style-type: none"> CBC with differential Signs and symptoms of bleeding (particularly when coadministered with anticoagulant or antiplatelet therapy) Monitor for cardiac arrhythmias Monitor for new infections 	<ul style="list-style-type: none"> Avoid concomitant use with strong CYP3A inhibitors or inducers. Dose reduction may be necessary with moderate CYP3A4 inhibitors. Avoid concomitant PPI use. H2-receptor antagonist should be administered 2 hours after acalabrutinib. 	<ul style="list-style-type: none"> The Panel recommends against the use of BTK inhibitors for the treatment of COVID-19, except in a clinical trial (Alli). Avoid use in patients with severe hepatic impairment. Patients with underlying cardiac risk factors, hypertension, or acute infections may be predisposed to atrial fibrillation. A list of clinical trials is available: Acalabrutinib

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Kinase Inhibitors , continued					
<i>Bruton's Tyrosine Kinase Inhibitors</i> , continued					
Ibrutinib	Dose for FDA-Approved Indications: <ul style="list-style-type: none"> Ibrutinib 420 mg or 560 mg PO once daily Dose for COVID-19: <ul style="list-style-type: none"> Dose and duration unknown 	<ul style="list-style-type: none"> Hemorrhage Cardiac arrhythmias Serious infections Cytopenias (thrombocytopenia, neutropenia, anemia) Hypertension Diarrhea Musculoskeletal pain Rash 	<ul style="list-style-type: none"> CBC with differential Blood pressure Signs and symptoms of bleeding (particularly when coadministered with anticoagulant or antiplatelet therapy) Monitor for cardiac arrhythmias Monitor for new infections 	<ul style="list-style-type: none"> Avoid concomitant use with strong CYP3A inhibitors or inducers. Dose reduction may be necessary with moderate CYP3A4 inhibitors. 	<ul style="list-style-type: none"> The Panel recommends against the use of BTK inhibitors for the treatment of COVID-19, except in a clinical trial (AIII). Avoid use in patients with severe baseline hepatic impairment. Dose modifications required in patients with mild or moderate hepatic impairment. Patients with underlying cardiac risk factors, hypertension, or acute infections may be predisposed to cardiac arrhythmias. A list of clinical trials is available: Ibrutinib
Zanubrutinib	Dose for FDA-Approved Indications: <ul style="list-style-type: none"> Zanubrutinib 160 mg PO twice daily or 320 mg PO once daily Dose for COVID-19: <ul style="list-style-type: none"> Dose and duration unknown 	<ul style="list-style-type: none"> Hemorrhage Cytopenias (neutropenia, thrombocytopenia, anemia, leukopenia) Atrial fibrillation and flutter Infection Rash Bruising Diarrhea Cough Musculoskeletal pain 	<ul style="list-style-type: none"> CBC with differential Signs and symptoms of bleeding Monitor for cardiac arrhythmias Monitor for new infections 	<ul style="list-style-type: none"> Avoid concomitant use with moderate or strong CYP3A inducers. Dose reduction required with moderate and strong CYP3A4 inhibitors. 	<ul style="list-style-type: none"> The Panel recommends against the use of BTK inhibitors for the treatment of COVID-19, except in a clinical trial (AIII). Dose reduction required in patients with severe hepatic impairment. A list of clinical trials is available: Zanubrutinib

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Kinase Inhibitors , continued					
<i>Janus Kinase Inhibitors</i>					
Baricitinib ¹⁷	Dose for Rheumatoid Arthritis: <ul style="list-style-type: none"> • <i>Adults:</i> Baricitinib 2 mg PO once daily Dose for COVID-19: ¹⁸ <ul style="list-style-type: none"> • <i>Adults:</i> Baricitinib 4 mg PO once daily for 14 days or until hospital discharge • <i>Children:</i> Limited data are available. Dose per the FDA EUA: <ul style="list-style-type: none"> • Aged ≥9 years: Baricitinib 4 mg PO once daily for 14 days or until hospital discharge • Aged ≥2 years to <9 years: Baricitinib 2 mg PO once daily for 14 days or until hospital discharge • See full prescribing information for dosage recommendations in patients with renal impairment or hepatic impairment.¹⁷ 	<ul style="list-style-type: none"> • Lymphoma and other malignancies • Thrombosis • Gastrointestinal perforation • Treatment-related changes in lymphocytes, neutrophils, Hgb, liver enzymes • HSV • Herpes zoster 	<ul style="list-style-type: none"> • CBC with differential • Renal function • Liver enzymes • Monitor for new infections 	<ul style="list-style-type: none"> • Dose modification is recommended when concurrently administering with a strong OAT3 inhibitor. • Avoid administration of live vaccines. 	<ul style="list-style-type: none"> • There are insufficient data for the Panel to recommend either for or against the use of baricitinib in combination with RDV for the treatment of COVID-19 in hospitalized patients, when corticosteroids can be used. • In the rare circumstance when corticosteroids cannot be used, the Panel recommends baricitinib in combination with RDV for the treatment of COVID-19 in hospitalized nonintubated patients who require oxygen supplementation (BIIa). • The Panel recommends against the use of baricitinib without RDV, except in a clinical trial (AIII). • There are insufficient data for the Panel to recommend either for or against the use of baricitinib in combination with corticosteroids for the treatment of COVID-19. Because both agents are potent immunosuppressants, there is a potential for an additive risk of infection. • Baricitinib is not recommended for patients with severe hepatic or renal impairment.

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Kinase Inhibitors , continued					
<i>Janus Kinase Inhibitors</i> , continued					
Baricitinib ¹⁷ , continued					<ul style="list-style-type: none"> • Baricitinib is available through the FDA EUA for the treatment of COVID-19 in combination with RDV for hospitalized adults and pediatric patients aged ≥2 years who require supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation.¹⁸ • A list of clinical trials is available: Baricitinib
Ruxolitinib	Dose for FDA-Approved Indications: <ul style="list-style-type: none"> • Ruxolitinib 5 mg– 20 mg PO twice daily Dose for COVID-19 in Clinical Trials: <ul style="list-style-type: none"> • Ruxolitinib 5 mg– 20 mg PO twice daily, for 14 days 	<ul style="list-style-type: none"> • Thrombocytopenia • Anemia • Neutropenia • Liver enzyme elevations • Risk of infection • Dizziness • Headache • Diarrhea • CPK elevation • Herpes zoster 	<ul style="list-style-type: none"> • CBC with differential • Liver enzymes • Monitor for new infections 	<ul style="list-style-type: none"> • Dose modifications required when administered with strong CYP3A4 inhibitors. • Avoid use with doses of fluconazole >200 mg. 	<ul style="list-style-type: none"> • The Panel recommends against the use of JAK inhibitors (other than baricitinib) for the treatment of COVID-19, except in a clinical trial (AIII). • Dose modification may be required in patients with moderate or severe renal impairment, hepatic impairment, or thrombocytopenia. • A list of clinical trials is available: Ruxolitinib

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Kinase Inhibitors , continued					
<i>Janus Kinase Inhibitors</i> , continued					
Tofacitinib	<p>Dose for FDA-Approved Indications:</p> <ul style="list-style-type: none"> • Tofacitinib 5 mg PO twice daily for rheumatoid and psoriatic arthritis • Tofacitinib 10 mg PO twice daily for ulcerative colitis <p>Dose for COVID-19:</p> <ul style="list-style-type: none"> • Dose and duration unknown; a planned COVID-19 clinical trial will evaluate tofacitinib 10 mg twice daily for 14 days. 	<ul style="list-style-type: none"> • Thrombotic events (pulmonary embolism, DVT, arterial thrombosis) • Anemia • Risk of infection • Gastrointestinal perforation • Diarrhea • Headache • Herpes zoster • Lipid elevations • Liver enzyme elevations • Lymphoma and other malignancies 	<ul style="list-style-type: none"> • CBC with differential • Liver enzymes • Monitor for new infections 	<ul style="list-style-type: none"> • Dose modifications required when administered with strong CYP3A4 inhibitors or when used with a moderate CYP3A4 inhibitor coadministered with a strong CYP2C19 inhibitor. • Avoid administration of live vaccines. 	<ul style="list-style-type: none"> • The Panel recommends against the use of JAK inhibitors (other than baricitinib) for the treatment of COVID-19, except in a clinical trial (AIII). • Avoid use in patients with ALC <500 cells/mm³, ANC <1,000 cells/mm³, or Hgb <9 grams/dL. • Dose modification may be required in patients with moderate or severe renal impairment or moderate hepatic impairment. • A list of clinical trials is available: Tofacitinib
Non-SARS-CoV-2 Specific Immunoglobulin					
Non-SARS-CoV-2 Specific Immunoglobulin	<ul style="list-style-type: none"> • Dose varies based on indication and formulation. 	<ul style="list-style-type: none"> • Allergic reactions including anaphylaxis • Renal failure • Thrombotic events • Aseptic meningitis syndrome • Hemolysis • TRALI • Transmission of infectious pathogens 	<ul style="list-style-type: none"> • Monitor for transfusion-related reactions • Monitor vital signs at baseline and during and after infusion • Discontinue if renal function deteriorates during treatment. 	<ul style="list-style-type: none"> • IVIG may interfere with immune response to certain vaccines. 	<ul style="list-style-type: none"> • The Panel recommends against the use of non-SARS-CoV-2 specific IVIG for the treatment of COVID-19, except in a clinical trial (AIII). This recommendation should not preclude the use of IVIG when otherwise indicated for the treatment of complications that arise during the course of COVID-19. • A list of clinical trials is available: Intravenous Immunoglobulin

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Non-SARS-CoV-2 Specific Immunoglobulin , continued					
Non-SARS-CoV-2 Specific Immunoglobulin , continued		<ul style="list-style-type: none"> • AEs may vary by formulation. • AEs may be increased with high-dose, rapid infusion, or in patients with underlying conditions. 			

Key: AE = adverse effect or adverse event; ALC = absolute lymphocyte count; ALT = alanine transaminase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BTK = Bruton's tyrosine kinase; CBC = complete blood count; CHF = congestive heart failure; CrCl = creatinine clearance; CPK = creatine phosphokinase; CRP = C-reactive protein; CYP = cytochrome P; DVT = deep vein thrombosis; EIND = Emergency Investigational New Drug; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; FiO₂ = fraction of inspired oxygen; HBV = hepatitis B; Hgb = hemoglobin; HSR = hypersensitivity reaction; HSV = herpes simplex virus; IFN = interferon; IL-1 = interleukin-1; IL-6 = interleukin-6; IV = intravenous; IVIG = intravenous immunoglobulin; JAK = Janus kinase; MERS = Middle East respiratory syndrome; OAT = organic anion transporter; PEG-IFN = pegylated interferon; PK = pharmacokinetic; PO = orally; PPI = proton pump inhibitor; REMAP-CAP = A Randomised, Embedded, Multi-Factorial, Adaptive Platform Trial for Community-Acquired Pneumonia; RDV = remdesivir; SARS = severe acute respiratory syndrome; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SQ = subcutaneous; TACO = transfusion-associated circulatory overload; TB = tuberculosis; the Panel = the COVID-19 Treatment Guidelines Panel; TNF = tumor necrosis factor; TRALI = transfusion-related acute lung injury; ULN = upper limit of normal

References

1. Randomised Evaluation of COVID-19 Therapy (RECOVERY). Low-cost dexamethasone reduces death by up to one third in hospitalised patients with severe respiratory complications of COVID-19. 2020; <https://www.recoverytrial.net/news/low-cost-dexamethasone-reduces-death-by-up-to-one-third-in-hospitalised-patients-with-severe-respiratory-complications-of-covid-19>. Accessed February 9, 2021.
2. Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid therapy for critically ill patients with Middle East respiratory syndrome. *Am J Respir Crit Care Med*. 2018;197(6):757-767. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29161116>.
3. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Med*. 2006;3(9):e343. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16968120>.
4. Stauffer WM, Alpern JD, Walker PF. COVID-19 and dexamethasone: a potential strategy to avoid steroid-related strongyloides hyperinfection. *JAMA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32761166>.

5. Liu J, Wang T, Cai Q, et al. Longitudinal changes of liver function and hepatitis B reactivation in COVID-19 patients with pre-existing chronic hepatitis B virus infection. *Hepatol Res*. 2020;50(11):1211-1221. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32761993>.
6. Centers for Disease Control and Prevention. Parasites—strongyloides: resources for health professionals. 2020; https://www.cdc.gov/parasites/strongyloides/health_professionals/index.html. Accessed February 9, 2021.
7. Omrani AS, Saad MM, Baig K, et al. Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: a retrospective cohort study. *Lancet Infect Dis*. 2014;14(11):1090-1095. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25278221>.
8. Shalhoub S, Farahat F, Al-Jiffri A, et al. IFN-alpha2a or IFN-beta1a in combination with ribavirin to treat Middle East respiratory syndrome coronavirus pneumonia: a retrospective study. *J Antimicrob Chemother*. 2015;70(7):2129-2132. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25900158>.
9. Zhou Q, Chen V, Shannon CP, et al. Interferon-alpha2b treatment for COVID-19. *Front Immunol*. 2020;11:1061. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32574262>.
10. Peginterferon alpha-2a (Pegasys) [package insert]. Food and Drug Administration. 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/103964s5270lbl.pdf.
11. Hung IFN, Lung KC, Tso EYK, 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. *Lancet*. 2020;395(10238):1695-1704. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32401715>.
12. Interferon beta-1a (Rebif) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/103780s5204lbl.pdf.
13. Sarilumab (Kevzara) [package insert]. Food and Drug Administration. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761037s001lbl.pdf.
14. Regeneron and Sanofi provide update on U.S. Phase 2/3 adaptive-designed trial of KEVZARA® (sarilumab) in hospitalized COVID-19 patients [press release]. 2020.
15. Tocilizumab (Actemra) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125276s127,125472s040lbl.pdf.
16. Siltuximab (Sylvant) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125496s018lbl.pdf.
17. Baricitinib (Olumiant) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/207924s001lbl.pdf.
18. Food and Drug Administration. Fact sheet for healthcare providers: Emergency Use Authorization (EUA) of baricitinib. 2020; <https://www.fda.gov/media/143823/download>. Accessed February 9, 2021.

Antithrombotic Therapy in Patients with COVID-19

Last Updated: February 11, 2021

Summary Recommendations

Laboratory Testing

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

Chronic Anticoagulant and Antiplatelet Therapy

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

Venous Thromboembolism Prophylaxis and Screening

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

Hospitalized Children With COVID-19

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

Treatment

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

Special Considerations During Pregnancy and Lactation

- If antithrombotic therapy is prescribed during pregnancy prior to a diagnosis of COVID-19, this therapy should be continued **(AIII)**.
- For pregnant patients hospitalized for severe COVID-19, prophylactic dose anticoagulation is recommended unless contraindicated (see below) **(BIII)**.

- Like for nonpregnant patients, VTE prophylaxis after hospital discharge **is not recommended** for pregnant patients (**AIII**). Decisions to continue VTE prophylaxis in the pregnant or postpartum patient after discharge should be individualized, considering concomitant VTE risk factors.
- Anticoagulation therapy use during labor and delivery requires specialized care and planning. It should be managed in pregnant patients with COVID-19 in a similar way as in pregnant patients with other conditions that require anticoagulation in pregnancy (**AIII**).
- Unfractionated heparin, low molecular weight heparin, and warfarin do not accumulate in breast milk and do not induce an anticoagulant effect in the newborn; therefore, they can be used by breastfeeding individuals with or without COVID-19 who require VTE prophylaxis or treatment (**AIII**). In contrast, use of direct-acting oral anticoagulants during pregnancy is not routinely recommended due to lack of safety data (**AIII**).

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

Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

Association Between COVID-19 and Thromboembolism

Infection with the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the resulting syndrome, COVID-19, have been associated with inflammation and a prothrombotic state, with increases in fibrin, fibrin degradation products, fibrinogen, and D-dimers.^{1,2} In some studies, elevations in these markers have been associated with worse clinical outcomes.^{3,4}

A number of studies have reported varying incidences of venous thromboembolism (VTE) in patients with COVID-19. A meta-analysis of studies in hospitalized patients with COVID-19 found an overall VTE prevalence of 14.1% (95% CI, 11.6–16.9).⁵ The VTE prevalence was higher in studies that used ultrasound screening (40.3%; 95% CI, 27.0–54.3) than in studies that did not (9.5%; 95% CI, 7.5–11.7). In randomized controlled trials conducted prior to the COVID-19 pandemic, the incidence of VTE in non-COVID-19 hospitalized patients who received VTE prophylaxis ranged from 0.3% to 1% for symptomatic VTE and from 2.8% to 5.6% for VTE overall.^{6–8} The VTE incidence in randomized trials in critically ill non-COVID-19 patients who received prophylactic dose anticoagulants ranged from 5% to 16%, and a prospective cohort study of critically ill patients with sepsis reported a VTE incidence of 37%.^{9–12} VTE guidelines for non-COVID-19 patients have recommended against routine screening ultrasounds in critically ill patients because no study has shown that this strategy reduces the rate of subsequent symptomatic thromboembolic complications.¹³ Although the incidence of thromboembolic events, especially pulmonary emboli, can be high among hospitalized patients with COVID-19, there are no published data demonstrating the clinical utility of routine surveillance for deep vein thrombosis using lower extremity ultrasound in this population.

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

There are limited prospective data demonstrating the safety and efficacy of using therapeutic doses of anticoagulants to prevent VTE in patients with COVID-19. A retrospective analysis of 2,773

hospitalized COVID-19 patients from a single center in the United States reported in-hospital mortality in 22.5% of patients who received therapeutic anticoagulation and 22.8% of patients who did not receive anticoagulation. The study further reported that in a subset of 395 mechanically ventilated patients, 29.1% of the patients who received anticoagulation and 62.7% of those who did not receive anticoagulation died. The study had important limitations: it lacked details on patient characteristics, indications for anticoagulant initiation, and descriptions of other therapies that the patients received that may have influenced mortality. In addition, the authors did not discuss the potential impact of survival bias on the study results. For these reasons, the data are not sufficient to influence standard of care, and this study further emphasizes the need for prospective trials to define the risks and potential benefits of therapeutic anticoagulation in patients with COVID-19.¹⁸ Three international trials (Antithrombotic Therapy to Ameliorate Complications of COVID-19 [ATTACC], Therapeutic Anticoagulation; Accelerating COVID-19 Therapeutic Interventions and Vaccines-4 [ACTIV-4], and the Randomized, Embedded, Multi-factorial Adaptive Platform Trial for Community-Acquired Pneumonia [REMAP-CAP]) compared the effectiveness of therapeutic dose anticoagulation and prophylactic dose anticoagulation in reducing the need for organ support over 21 days in moderately ill or critically ill adults hospitalized for COVID-19. The need for organ support was defined as requiring high-flow nasal oxygen, invasive or noninvasive mechanical ventilation, vasopressor therapy, or extracorporeal membrane oxygenation (ECMO). The trials paused enrollment of patients requiring intensive care unit (ICU)-level care after an interim pooled analysis demonstrated futility of therapeutic anticoagulation in improving organ support, and a concern for safety. The results of the interim analysis are available on the [ATTACC website](#). Unblinded data and additional study outcomes, including the occurrence of thrombosis, are expected to be reported soon.¹⁹

A small, single-center randomized trial (n = 20) compared therapeutic and prophylactic anticoagulation in mechanically ventilated patients with D-dimers >1,000 µg/L (as measured by the VIDAS D-dimer Exclusion II assay). Only the patients treated with therapeutic anticoagulation showed improvement in the ratio of arterial oxygen partial pressure of oxygen to fraction of inspired oxygen (PaO₂/FiO₂). The number of ventilator-free days was higher in the therapeutic anticoagulation arm than in the prophylactic anticoagulation arm (15 days [IQR 6–16] vs. 0 days [IQR 0–11]; *P* = 0.028). There was no difference between the arms in in-hospital or 28-day mortality. Two patients treated with therapeutic anticoagulation had minor bleeding, and two patients in each arm experienced thrombosis.²⁰ Additional evidence from large, multicenter trials is needed, and the trial results are expected soon.

Several randomized controlled trials have been developed to evaluate the risks and benefits of anticoagulation in patients with COVID-19 (visit [ClinicalTrials.gov](#) for the current list of trials). Guidelines about coagulopathy and prevention and management of VTE in patients with COVID-19 have been released by multiple organizations, including the Anticoagulation Forum,²¹ the American College of Chest Physicians,²² the American Society of Hematology,²³ the International Society of Thrombosis and Haemostasis (ISTH),²⁴ the Italian Society on Thrombosis and Haemostasis,²⁵ and the Royal College of Physicians.²⁶ In addition, a paper that outlines issues related to thrombotic disease with implications for prevention and therapy has been endorsed by the ISTH, the North American Thrombosis Forum, the European Society of Vascular Medicine, and the International Union of Angiology.²⁷

All of the guidelines referenced above agree that hospitalized patients with COVID-19 should receive prophylactic dose anticoagulation for VTE. Some guidelines note that intermediate dose anticoagulation can be considered for critically ill patients.^{21,23,26,28} Given the variation in VTE incidence and the unknown risk of bleeding in critically ill patients with COVID-19, the COVID-19 Treatment Guidelines Panel and guideline panels of the American Society of Hematology and the American College of Chest Physician recommend treating all hospitalized patients with COVID-19, including critically ill patients, with prophylactic dose anticoagulation.^{22,29} Results from clinical trials that assess the safety and efficacy

of different anticoagulant doses will provide further information on the best prophylactic strategies for patients with COVID-19.

Monitoring Coagulation Markers in Patients With COVID-19

In nonhospitalized patients with COVID-19, markers of coagulopathy, such as D-dimer level, prothrombin time, fibrinogen level, and platelet count, should not routinely be obtained (**AIII**). Although abnormalities in these coagulation markers have been associated with worse outcomes, prospective data demonstrating that the markers can be used to predict the risk of VTE in those who are asymptomatic or who have mild SARS-CoV-2 infection is lacking.

In hospitalized patients with COVID-19, hematologic and coagulation parameters are commonly measured; however, there are currently insufficient data to recommend either for or against using such data to guide management decisions.

Managing Antithrombotic Therapy in Patients With COVID-19

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

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

Chronic Anticoagulant or Antiplatelet Therapy

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

Patients with COVID-19 Who Are Managed as Outpatients

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

Hospitalized Patients With COVID-19

For hospitalized patients with COVID-19, prophylactic dose anticoagulation should be prescribed unless contraindicated (e.g., a patient has active hemorrhage or severe thrombocytopenia) (**AIII**). Although data supporting this recommendation are limited, a retrospective study showed reduced mortality in patients who received prophylactic anticoagulation, particularly if the patient had a sepsis-induced coagulopathy score ≥ 4 .⁴ For those without COVID-19, anticoagulant or antiplatelet therapy should not be used to prevent arterial thrombosis outside of the standard of care (**AIII**). Anticoagulation is routinely used to prevent arterial thromboembolism in patients with heart arrhythmias. Although there are reports of strokes and myocardial infarction in patients with COVID-19, the incidence of these events is unknown.

When imaging is not possible, patients with COVID-19 who experience an incident thromboembolic event or who are highly suspected to have thromboembolic disease should be managed with therapeutic doses of anticoagulant therapy as per the standard of care for patients without COVID-19 (AIII).

There are currently insufficient data to recommend either for or against the use of thrombolytic agents or higher than the prophylactic dose of anticoagulation for VTE prophylaxis for hospitalized patients with COVID-19 outside of a clinical trial. Three international trials (ACTIV-4, REMAP-CAP, and ATTACC) compared the effectiveness of therapeutic dose anticoagulation and prophylactic dose anticoagulation in reducing the need for organ support over 21 days in moderately ill or critically ill adults hospitalized for COVID-19. The need for organ support was defined as requiring high-flow nasal oxygen, invasive or noninvasive mechanical ventilation, vasopressor therapy, or ECMO. The trials paused enrollment of patients requiring ICU-level care at enrollment after an interim pooled analysis demonstrated futility of therapeutic anticoagulation in reducing the need for organ support and a concern for safety. The results of the interim analysis are available on the [ATTACC website](#). Unblinded data and additional study outcomes, including the occurrence of thrombosis, are expected to be reported soon.¹⁹

Although there is evidence that multi-organ failure is more likely in patients with sepsis who develop coagulopathy,³⁰ there is no convincing evidence to show that any specific antithrombotic treatment will influence outcomes in those with or without COVID-19. Participation in randomized trials is encouraged.

Patients with COVID-19 who require ECMO or continuous renal replacement therapy or who have thrombosis of catheters or extracorporeal filters should be treated as per the standard institutional protocols for those without COVID-19 (AIII).

Hospitalized Children With COVID-19

A recent meta-analysis of publications on COVID-19 in children did not discuss VTE.³¹ Indications for VTE prophylaxis in hospitalized children with COVID-19 should be the same as those for hospitalized children without COVID-19 (BIII).

Patients With COVID-19 Who Are Discharged from the Hospital

VTE prophylaxis after hospital discharge **is not recommended** for patients with COVID-19 (AIII). For certain high-VTE risk patients without COVID-19, post-discharge prophylaxis has been shown to be beneficial. The Food and Drug Administration approved the use of rivaroxaban 10 mg daily for 31 to 39 days in these patients.^{32,33} Inclusion criteria for the trials that studied post-discharge VTE prophylaxis included:

- Modified International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) VTE risk score ≥ 4 ; *or*
- Modified IMPROVE VTE risk score ≥ 2 and D-dimer level > 2 times the upper limit of normal.³²

Any decision to use post-discharge VTE prophylaxis for patients with COVID-19 should include consideration of the individual patient's risk factors for VTE, including reduced mobility, bleeding risks, and feasibility. Participation in clinical trials is encouraged.

Special Considerations During Pregnancy and Lactation

Because pregnancy is a hypercoagulable state, the risk of thromboembolism is greater in pregnant individuals than in nonpregnant individuals.³⁴ It is not yet known whether COVID-19 increases this risk. In several cohort studies of pregnant women with COVID-19 in the United States and Europe,

VTE was not reported as a complication even among women with severe disease, although the receipt of prophylactic or therapeutic anticoagulation varied across the studies.³⁵⁻³⁷ The American College of Obstetricians and Gynecologists (ACOG) advises that, although there are no data for or against thromboprophylaxis in the setting of COVID-19 in pregnancy, VTE prophylaxis can reasonably be considered for pregnant women hospitalized with COVID-19, particularly for those who have severe disease.³⁸ If there are no contraindications to use, the Society of Maternal Fetal Medicine recommends prophylactic heparin or low molecular weight heparin in critically ill or mechanically ventilated pregnant patients.³⁹ Several professional societies, including the American Society of Hematology and ACOG, have guidelines that specifically address the management of VTE in the context of pregnancy.^{40,41} If delivery is threatened, or if there are other risks for bleeding, the risk of bleeding may outweigh the potential benefit of VTE prophylaxis in pregnancy.

There are no data on the use of scoring systems to predict VTE risk in pregnant individuals. Additionally, during pregnancy, the D-dimer level may not be a reliable predictor of VTE because there is a physiologic increase of D-dimer levels throughout gestation.⁴²⁻⁴⁴

In general, the preferred anticoagulants during pregnancy are heparin compounds. Because of its reliability and ease of administration, low-molecular weight heparin is recommended, rather than unfractionated heparin, for the prevention and treatment of VTE in pregnancy.⁴¹

Direct-acting anticoagulants are not routinely used during pregnancy due to the lack of safety data in pregnant individuals.⁴⁰ The use of warfarin to prevent or treat VTE should be avoided in pregnant individuals, regardless of their COVID-19 status, and especially during the first trimester due to the concern for teratogenicity.

Specific recommendations for pregnant or lactating individuals with COVID-19 include:

- If antithrombotic therapy is prescribed during pregnancy prior to a diagnosis of COVID-19, this therapy should be continued (**AIII**).
- For pregnant patients hospitalized for severe COVID-19, prophylactic dose anticoagulation is recommended unless contraindicated (**BIII**).
- Like for nonpregnant patients, VTE prophylaxis after hospital discharge **is not recommended** for pregnant patients (**AIII**). Decisions to continue VTE prophylaxis in the pregnant or postpartum patient should be individualized, considering concomitant VTE risk factors.
- Anticoagulation therapy use during labor and delivery requires specialized care and planning. It should be managed in pregnant patients with COVID-19 in a similar way as in pregnant patients with other conditions that require anticoagulation in pregnancy (**AIII**).
- Unfractionated heparin, low molecular weight heparin, and warfarin do not accumulate in breast milk and do not induce an anticoagulant effect in the newborn; therefore, they can be used by breastfeeding women with or without COVID-19 who require VTE prophylaxis or treatment (**AIII**). In contrast, use of direct-acting oral anticoagulants during pregnancy is not routinely recommended due to lack of safety data (**AIII**).⁴⁰

References

1. Han H, Yang L, Liu R, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. *Clin Chem Lab Med*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32172226>.
2. Driggin E, Madhavan MV, Bikdeli B, et al. Cardiovascular considerations for patients, health care workers, and health systems during the coronavirus disease 2019 (COVID-19) pandemic. *J Am Coll Cardiol*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32201335>.

3. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32109013>.
4. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost*. 2020;18(5):1094-1099. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32220112>.
5. Nopp S, Moik F, Jilma B, Pabinger I, Ay C. Risk of venous thromboembolism in patients with COVID-19: a systematic review and meta-analysis. *Res Pract Thromb Haemost*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33043231>.
6. Cohen AT, Davidson BL, Gallus AS, et al. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. *BMJ*. 2006;332(7537):325-329. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16439370>.
7. Leizorovicz A, Cohen AT, Turpie AG, et al. Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. *Circulation*. 2004;110(7):874-879. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15289368>.
8. Samama MM, Cohen AT, Darmon JY, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in Medical Patients with Enoxaparin Study Group. *N Engl J Med*. 1999;341(11):793-800. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10477777>.
9. Fraisse F, Holzapfel L, Couland JM, et al. Nadroparin in the prevention of deep vein thrombosis in acute decompensated COPD. The Association of Non-University Affiliated Intensive Care Specialist Physicians of France. *Am J Respir Crit Care Med*. 2000;161(4 Pt 1):1109-1114. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10764298>.
10. PROTECT Investigators for the Canadian Critical Care Trials Group and the Australian and New Zealand Intensive Care Society Clinical Trials Group, et al. Dalteparin versus unfractionated heparin in critically ill patients. *N Engl J Med*. 2011;364(14):1305-1314. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21417952>.
11. Shorr AF, Williams MD. Venous thromboembolism in critically ill patients. Observations from a randomized trial in sepsis. *Thromb Haemost*. 2009;101(1):139-144. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19132200>.
12. Kaplan D, Casper TC, Elliott CG, et al. VTE incidence and risk factors in patients with severe sepsis and septic shock. *Chest*. 2015;148(5):1224-1230. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26111103>.
13. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2 Suppl):e195S-e226S. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22315261>.
14. American Society of Hematology. Should DOACs, LMWH, UFH, Fondaparinux, Argatroban, or Bivalirudin at intermediate-intensity or therapeutic-intensity vs. prophylactic intensity be used for patients with COVID-19 related critical illness who do not have suspected or confirmed VTE? 2020. Available at: <https://guidelines.ash.gradepro.org/profile/3CQ7J0SWt58>. Accessed December 7, 2020.
15. Roberts LN, Whyte MB, Georgiou L, et al. Postdischarge venous thromboembolism following hospital admission with COVID-19. *Blood*. 2020;136(11):1347-1350. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32746455>.
16. Engelen MM, Vanassche T, Balthazar T, et al. Incidence of venous thromboembolism in patients discharged after COVID-19 Hospitalization [abstract]. *Res Pract Thromb Haemost*. 2020;4 (Suppl 1). Available at: <https://abstracts.isth.org/abstract/incidence-of-venous-thromboembolism-in-patients-discharged-after-covid-19-hospitalisation/>.
17. Patell R, Bogue T, Koshy A, et al. Postdischarge thrombosis and hemorrhage in patients with COVID-19. *Blood*. 2020;136(11):1342-1346. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32766883>.

18. Paranjpe I, Fuster V, Lala A, et al. Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. *Journal of the American College of Cardiology*. 2020;In press. Available at: <https://www.sciencedirect.com/science/article/pii/S0735109720352189?via%3Dihub>.
19. NIH ACTIV Trial of blood thinners pauses enrollment of critically ill COVID-19 patients [press release]. 2020. Available at: <https://www.nih.gov/news-events/news-releases/nih-activ-trial-blood-thinners-pauses-enrollment-critically-ill-covid-19-patients>. Accessed February 8, 2021.
20. Lemos ACB, do Espirito Santo DA, Salvetti MC, et al. Therapeutic versus prophylactic anticoagulation for severe COVID-19: a randomized Phase II clinical trial (HESACOVID). *Thromb Res*. 2020;196:359-366. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32977137>.
21. Barnes GD, Burnett A, Allen A, et al. Thromboembolism and anticoagulant therapy during the COVID-19 pandemic: interim clinical guidance from the anticoagulation forum. *J Thromb Thrombolysis*. 2020;50(1):72-81. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32440883>.
22. Moores LK, Tritschler T, Brosnahan S, et al. Prevention, diagnosis, and treatment of VTE in patients with coronavirus disease 2019: CHEST guideline and expert panel report. *Chest*. 2020;158(3):1143-1163. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32502594>.
23. American Society of Hematology. ASH guidelines on use of anticoagulation in patients with COVID-19. 2020. Available at: <https://www.hematology.org/education/clinicians/guidelines-and-quality-care/clinical-practice-guidelines/venous-thromboembolism-guidelines/ash-guidelines-on-use-of-anticoagulation-in-patients-with-covid-19>. Accessed November 13, 2020.
24. Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost*. 2020;18(5):1023-1026. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32338827>.
25. Marietta M, Ageno W, Artoni A, et al. COVID-19 and haemostasis: a position paper from Italian Society on Thrombosis and Haemostasis (SISSET). *Blood Transfus*. 2020;18(3):167-169. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32281926>.
26. Royal College of Physicians. Clinical guide for the prevention, detection and management of thromboembolic disease in patients with COVID-19. 2020. Available at: <https://icmanaesthesiacovid-19.org/clinical-guide-prevention-detection-and-management-of-vte-in-patients-with-covid-19>. Accessed November 13, 2020.
27. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and thrombotic or thromboembolic disease: Implications for prevention, antithrombotic therapy, and follow-up. *J Am Coll Cardiol*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32311448>.
28. Spyropoulos AC, Levy JH, Ageno W, et al. Scientific and Standardization Committee communication: clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost*. 2020;18(8):1859-1865. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32459046>.
29. American Society of Hematology. COVID-19 and VTE/anticoagulation: frequently asked questions. 2020. Available at: <https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation>. Accessed February 8, 2021.
30. Iba T, Nisio MD, Levy JH, Kitamura N, Thachil J. New criteria for sepsis-induced coagulopathy (SIC) following the revised sepsis definition: a retrospective analysis of a nationwide survey. *BMJ Open*. 2017;7(9):e017046. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28963294>.
31. Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. *Acta Paediatr*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32202343>.
32. Spyropoulos AC, Lipardi C, Xu J, et al. Modified IMPROVE VTE risk score and elevated D-dimer identify a high venous thromboembolism risk in acutely ill medical population for extended thromboprophylaxis. *TH Open*. 2020;4(1):e59-e65. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32190813>.
33. Cohen AT, Harrington RA, Goldhaber SZ, et al. Extended thromboprophylaxis with betrixaban in acutely ill

- medical patients. *N Engl J Med*. 2016;375(6):534-544. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27232649>.
34. Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, Melton LJ 3rd. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. *Ann Intern Med*. 2005;143(10):697-706. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16287790>.
 35. Breslin N, Baptiste C, Gyamfi-Bannerman C, et al. Coronavirus disease 2019 infection among asymptomatic and symptomatic pregnant women: two weeks of confirmed presentations to an affiliated pair of New York City hospitals. *Am J Obstet Gynecol MFM*. 2020;2(2):100118. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32292903>.
 36. Knight M, Bunch K, Vousden N, et al. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study. *BMJ*. 2020;369:m2107. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32513659>.
 37. Delahoy MJ, Whitaker M, O'Halloran A, et al. Characteristics and maternal and birth outcomes of hospitalized pregnant women with laboratory-confirmed COVID-19 - COVID-NET, 13 states, March 1–August 22, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(38):1347-1354. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32970655>.
 38. The American College of Obstetricians and Gynecologists. COVID-19 FAQs for obstetrician-gynecologists, obstetrics. 2020. Available at: <https://www.acog.org/clinical-information/physician-faqs/covid-19-faqs-for-ob-gyns-obstetrics>. Accessed February 8, 2021.
 39. Society for Maternal Fetal Medicine. Management considerations for pregnant patients with COVID-19. 2020. Available at: https://s3.amazonaws.com/cdn.smfm.org/media/2336/SMFM_COVID_Management_of_COVID_pos_preg_patients_4-30-20_final.pdf. Accessed February 8, 2021.
 40. Bates SM, Rajasekhar A, Middeldorp S, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy. *Blood Adv*. 2018;2(22):3317-3359. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30482767>.
 41. ACOG practice bulletin no. 196 summary: thromboembolism in pregnancy. *Obstet Gynecol*. 2018;132(1):243-248. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29939933>.
 42. Wang M, Lu S, Li S, Shen F. Reference intervals of D-dimer during the pregnancy and puerperium period on the STA-R evolution coagulation analyzer. *Clin Chim Acta*. 2013;425:176-180. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23954836>.
 43. Reger B, Peterfalvi A, Litter I, et al. Challenges in the evaluation of D-dimer and fibrinogen levels in pregnant women. *Thromb Res*. 2013;131(4):e183-187. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23481480>.
 44. Hu W, Wang Y, Li J, et al. The predictive value of D-dimer test for venous thromboembolism during puerperium: a prospective cohort study. *Clin Appl Thromb Hemost*. 2020;26:1076029620901786. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32090610>.

Supplements

Last Updated: February 11, 2021

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

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

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

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

Vitamin C

Last Updated: November 3, 2020

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

Recommendation for Non-Critically Ill Patients With COVID-19

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

Rationale

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

Recommendation for Critically Ill Patients With COVID-19

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

Rationale

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

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

Intravenous Vitamin C Alone

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

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

Intravenous Vitamin C Plus Thiamine With or Without Hydrocortisone

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

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

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

Other Considerations

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

References

1. Wei XB, Wang ZH, Liao XL, et al. Efficacy of vitamin C in patients with sepsis: an updated meta-analysis. *Eur J Pharmacol*. 2020;868:172889. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31870831>.
2. Fisher BJ, Seropian IM, Kraskauskas D, et al. Ascorbic acid attenuates lipopolysaccharide-induced acute lung injury. *Crit Care Med*. 2011;39(6):1454-1460. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21358394>.
3. Fowler AA, 3rd, Syed AA, Knowlson S, et al. Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. *J Transl Med*. 2014;12:32. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24484547>.
4. Fowler AA, 3rd, Truwit JD, Hite RD, et al. Effect of vitamin C infusion on organ failure and biomarkers of inflammation and vascular injury in patients with sepsis and severe acute respiratory failure: the CITRIS-ALI randomized clinical trial. *JAMA*. 2019;322(13):1261-1270. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31573637>.
5. Fowler AA, 3rd, Fisher BJ, Kashiouris MG. Vitamin C for sepsis and acute respiratory failure—reply. *JAMA*. 2020;323(8):792-793. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32096845>.
6. Marik PE, Khangoora V, Rivera R, Hooper MH, Catravas J. Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock: a retrospective before-after study. *Chest*. 2017;151(6):1229-1238. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27940189>.
7. Kim WY, Jo EJ, Eom JS, et al. Combined vitamin C, hydrocortisone, and thiamine therapy for patients with severe pneumonia who were admitted to the intensive care unit: propensity score-based analysis of a before-after cohort study. *J Crit Care*. 2018;47:211-218. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30029205>.
8. Fujii T, Luethi N, Young PJ, et al. Effect of vitamin C, hydrocortisone, and thiamine vs hydrocortisone alone on time alive and free of vasopressor support among patients with septic shock: the VITAMINS randomized clinical trial. *JAMA*. 2020;323(5):423-431. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31950979>.
9. Chang P, Liao Y, Guan J, et al. Combined treatment with hydrocortisone, vitamin c, and thiamine for sepsis and septic shock: a randomized controlled trial. *Chest*. 2020;158(1):174-182. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32243943>.
10. Iglesias J, Vassallo AV, Patel VV, Sullivan JB, Cavanaugh J, Elbaga Y. Outcomes of metabolic resuscitation

using ascorbic acid, thiamine, and glucocorticoids in the early treatment of sepsis: the ORANGES trial. *Chest*. 2020;158(1):164-173. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32194058>.

11. Hwang SY, Ryoo SM, Park JE, et al. Combination therapy of vitamin C and thiamine for septic shock: a multi-centre, double-blinded randomized, controlled study. *Intensive Care Med*. 2020; Published online ahead of print. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32780166>.
12. Moskowitz A, Huang DT, Hou PC, et al. Effect of ascorbic acid, corticosteroids, and thiamine on organ injury in septic shock: the ACTS randomized clinical trial. *JAMA*. 2020;324(7):642-650. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32809003>.
13. Hager DN, Martin GS, Sevransky JE, Hooper MH. Glucometry when using vitamin C in sepsis: a note of caution. *Chest*. 2018;154(1):228-229. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30044741>.

Vitamin D

Last Updated: July 17, 2020

Recommendation

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

General Information

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

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

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

Vitamin D and COVID-19

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

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

References

1. Aranow C. Vitamin D and the immune system. *J Investig Med*. 2011;59(6):881-886. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21527855>.
2. Forrest KY, Stuhldreher WL. Prevalence and correlates of vitamin D deficiency in US adults. *Nutr Res*. 2011;31(1):48-54. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21310306>.
3. Lu D, Zhang J, Ma C, et al. Link between community-acquired pneumonia and vitamin D levels in older patients. *Z Gerontol Geriatr*. 2018;51(4):435-439. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/28477055>.

4. Science M, Maguire JL, Russell ML, Smieja M, Walter SD, Loeb M. Low serum 25-hydroxyvitamin D level and risk of upper respiratory tract infection in children and adolescents. *Clin Infect Dis*. 2013;57(3):392-397. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23677871>.
5. Fisher SA, Rahimzadeh M, Brierley C, et al. The role of vitamin D in increasing circulating T regulatory cell numbers and modulating T regulatory cell phenotypes in patients with inflammatory disease or in healthy volunteers: a systematic review. *PLoS One*. 2019;14(9):e0222313. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31550254>.
6. Martineau AR, Jolliffe DA, Hooper RL, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. *BMJ*. 2017;356:i6583. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28202713>.
7. Amrein K, Schnedl C, Holl A, et al. Effect of high-dose vitamin D3 on hospital length of stay in critically ill patients with vitamin D deficiency: the VITdAL-ICU randomized clinical trial. *JAMA*. 2014;312(15):1520-1530. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25268295>.
8. National Heart Lung and Blood Institute PCTN, Ginde AA, et al. Early high-dose vitamin D3 for critically ill, vitamin D-deficient patients. *N Engl J Med*. 2019;381(26):2529-2540. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31826336>.
9. Ross AC, Taylor CL, Yaktine AL, Del Valle HB, eds. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington (DC): National Academies Press (US); 2011. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK56070/>.

Zinc Supplementation and COVID-19

Last Updated: February 11, 2021

Recommendations

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

Rationale

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

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

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

Clinical Data

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

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

Results

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

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

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

Limitations

- This study had a relatively small sample size.

Interpretation

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

Observational Study of Zinc Supplementation in Hospitalized Patients

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

Results

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

Limitations

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

Interpretation

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

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

This study has not been peer reviewed.

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

Results

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

Limitations

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

Interpretation

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

References

1. te Velthuis AJ, van den Worm SH, Sims AC, Baric RS, Snijder EJ, van Hemert MJ. Zn(2+) inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. *PLoS Pathog.* 2010;6(11):e1001176. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21079686>.
2. Xue J, Moyer A, Peng B, Wu J, Hannafon BN, Ding WQ. Chloroquine is a zinc ionophore. *PLoS One.* 2014;9(10):e109180. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25271834>.
3. Calder PC, Carr AC, Gombart AF, Eggersdorfer M. Optimal nutritional status for a well-functioning immune system is an important factor to protect against viral infections. *Nutrients.* 2020;12(4). Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32340216>.
4. Hambridge K. The management of lipohypertrophy in diabetes care. *Br J Nurs.* 2007;16(9):520-524. Available

at: <https://www.ncbi.nlm.nih.gov/pubmed/17551441>.

5. National Institutes of Health. Office of Dietary Supplements. Zinc fact sheet for health professionals. 2020. Available at: <https://ods.od.nih.gov/factsheets/Zinc-HealthProfessional/>. Accessed January 25, 2021.
6. Myint ZW, Oo TH, Thein KZ, Tun AM, Saeed H. Copper deficiency anemia: review article. *Ann Hematol*. 2018;97(9):1527-1534. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29959467>.
7. Kumar N. Copper deficiency myelopathy (human swayback). *Mayo Clin Proc*. 2006;81(10):1371-1384. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17036563>.
8. Abd-Elsalam S, Soliman S, Esmail ES, et al. Do zinc supplements Enhance the clinical efficacy of hydroxychloroquine?: a randomized, multicenter trial. *Biol Trace Elem Res*. 2020;Published online ahead of print. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33247380>.
9. Yao JS, Paguio JA, Dee EC, et al. The minimal effect of zinc on the survival of hospitalized patients with COVID-19: an observational study. *Chest*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32710890>.
10. Frontera JA, Rahimian JO, Yaghi S, et al. Treatment with zinc is associated with reduced in-hospital mortality among COVID-19 patients: a multi-center cohort study. *Res Sq*. 2020;Preprint. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33140042>.

Considerations for Certain Concomitant Medications in Patients with COVID-19

Last Updated: July 30, 2020

Summary Recommendations

Angiotensin-Converting Enzyme (ACE) Inhibitors and Angiotensin Receptor Blockers (ARBs)

- Persons with COVID-19 who are prescribed ACE inhibitors or ARBs for cardiovascular disease (or other indications) should continue these medications **(AIII)**.
- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of ACE inhibitors or ARBs for the treatment of COVID-19, except in a clinical trial **(AIII)**.

Corticosteroids

For management of COVID-19

- On the basis of the preliminary report from the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial, the COVID-19 Treatment Guidelines Panel (the Panel) recommends using **dexamethasone** 6 mg per day for up to 10 days for the treatment of COVID-19 in patients who are mechanically ventilated **(AI)** and in patients who require supplemental oxygen but who are not mechanically ventilated **(BI)**.
- The Panel **recommends against** using **dexamethasone** for the treatment of COVID-19 in patients who do not require supplemental oxygen **(AI)**.
- If dexamethasone is not available, the Panel recommends using alternative glucocorticoids such as **prednisone**, **methylprednisolone**, or **hydrocortisone** **(AIII)**.
- See [Corticosteroids](#) for a detailed discussion of these recommendations.

For patients on chronic corticosteroids

- Oral corticosteroid therapy that was used prior to COVID-19 diagnosis for another underlying condition (e.g., primary or secondary adrenal insufficiency, rheumatological diseases) should not be discontinued **(AIII)**. On a case-by-case basis, supplemental or stress-dose steroids may be indicated **(AIII)**.
- Inhaled corticosteroids that are used daily for patients with asthma and chronic obstructive pulmonary disease for control of airway inflammation should not be discontinued in patients with COVID-19 **(AIII)**.

Considerations in pregnancy

- Given the potential benefit of decrease in maternal mortality and the low risk of fetal adverse effects for this short course of therapy, the Panel recommends using **dexamethasone** in pregnant women with COVID-19 who are mechanically ventilated **(AIII)** or who require supplemental oxygen but who are not mechanically ventilated **(BIII)**.

HMG-CoA Reductase Inhibitors (Statins)

- Persons with COVID-19 who are prescribed statin therapy for the treatment or prevention of cardiovascular disease should continue these medications **(AIII)**.
- The Panel **recommends against** the use of statins for the treatment of COVID-19, except in a clinical trial **(AIII)**.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

- Persons with COVID-19 who are taking NSAIDs for a comorbid condition should continue therapy as previously directed by their physician **(AIII)**.
- The Panel recommends that there be no difference in the use of antipyretic strategies (e.g., with acetaminophen or NSAIDs) between patients with or without COVID-19 **(AIII)**.

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

Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

Recommendations

- Persons with COVID-19 who are prescribed angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) for cardiovascular disease (or other indications) should continue these medications (**AIII**).
- The COVID-19 Treatment Guidelines Panel (the Panel) recommends against the use of ACE inhibitors or ARBs for the treatment of COVID-19, except in a clinical trial (**AIII**).

Angiotensin-converting enzyme 2 (ACE2) is the cell surface receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It has been hypothesized¹ that the modulation of ACE2 associated with ACE inhibitors or ARBs could suppress or enhance SARS-CoV-2 replication.² Investigations of the role of ARBs and recombinant human ACE2 in the treatment and prevention of SARS-CoV-2 infection are underway.³

Whether these medications are helpful, harmful, or neutral in the pathogenesis of SARS-CoV-2 infection is unclear. Currently, there is a lack of sufficient clinical evidence demonstrating that ACE inhibitors or ARBs have any impact on the susceptibility of individuals to SARS-CoV-2 or on the severity or outcomes of infection. The Panel's recommendation against the use of these medications for the treatment of COVID-19 is in accord with a joint statement of the American Heart Association, the Heart Failure Society of America, and the American College of Cardiology.³

Corticosteroids

It has been proposed that the anti-inflammatory effects of corticosteroids have a potential therapeutic role in suppressing cytokine-related lung injury in patients with COVID-19.⁴ Data reported for other respiratory infections have shown that systemic corticosteroids can affect the pathogenesis of these infections in various ways. In outbreaks of other novel coronavirus infections^{5,6} (i.e., Middle East respiratory syndrome [MERS] and SARS), corticosteroid therapy was associated with delayed virus clearance. In severe pneumonia caused by influenza, corticosteroid therapy may lead to worse clinical outcomes, including secondary bacterial infection and mortality.⁷

Preliminary clinical trial data from a large, randomized, open-label trial suggest that dexamethasone reduces mortality in hospitalized patients with COVID-19 who require mechanical ventilation or supplemental oxygen.⁸ The recommendations for using corticosteroids in patients with COVID-19 depend on the severity of illness. Before initiating dexamethasone, clinicians should review the patient's medical history and assess the potential risks and benefits of administering corticosteroids to the patient.

For Management of COVID-19

Recommendations

- On the basis of the preliminary report from the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial, the Panel recommends using **dexamethasone** 6 mg per day for up to 10 days for the treatment of COVID-19 in patients who are mechanically ventilated (**AI**) and in patients who require supplemental oxygen but who are not mechanically ventilated (**BI**).
- The Panel **recommends against** using **dexamethasone** for the treatment of COVID-19 in patients who do not require supplemental oxygen (**AI**).
- If dexamethasone is not available, the Panel recommends using alternative glucocorticoids such as **prednisone**, **methylprednisolone**, or **hydrocortisone** (**AIII**).

See [Corticosteroids](#) for a detailed discussion of these recommendations.

Patients on Chronic Systemic Corticosteroid Therapy

Patients with COVID-19 may also be receiving systemic corticosteroid therapy for a variety of underlying conditions.

Recommendation

- Oral corticosteroid therapy that was used prior to COVID-19 diagnosis for another underlying condition (e.g., primary or secondary adrenal insufficiency, rheumatological diseases) should not be discontinued (**AIII**).⁹ On a case-by-case basis, supplemental or stress-dose steroids may be indicated (**AIII**).

Patients on Inhaled Corticosteroids

Recommendation

- Inhaled corticosteroids that are used daily for patients with asthma and chronic obstructive pulmonary disease for control of airway inflammation should not be discontinued in patients with COVID-19 (**AIII**). No studies to date have investigated the relationship between inhaled corticosteroids in these settings and virus acquisition, severity of illness, or viral transmission.

Pregnancy Considerations

A short course of betamethasone and dexamethasone, which are corticosteroids known to cross the placenta, is routinely used to hasten fetal lung maturity and decrease the risk of neonatal respiratory distress syndrome in the premature infant with threatened delivery.^{10,11}

- Given the potential benefit of decrease in maternal mortality and the low risk of fetal adverse effects for this short course of therapy, the Panel recommends using **dexamethasone** in pregnant women with COVID-19 who are mechanically ventilated (**AIII**) or who require supplemental oxygen but who are not mechanically ventilated (**BIII**).

HMG-CoA Reductase Inhibitors (Statins)

Recommendations

- Persons with COVID-19 who are prescribed statin therapy for the treatment or prevention of cardiovascular disease should continue these medications (**AIII**).
- The Panel **recommends against** the use of statins for the treatment of COVID-19, except in a clinical trial (**AIII**).

HMG-CoA reductase inhibitors, or statins, affect ACE2 as part of their function in reducing endothelial dysfunction. It has been proposed that these agents have a potential role in managing patients with severe COVID-19.¹² Observational studies have reported that statin therapy may reduce cardiovascular morbidity in patients admitted with other respiratory infections, such as influenza and bacterial pneumonia.

Nonsteroidal Anti-Inflammatory Drugs

Recommendations

- Persons with COVID-19 who are taking nonsteroidal anti-inflammatory drugs (NSAIDs) for a comorbid condition should continue therapy as previously directed by their physician (**AIII**).
- The Panel recommends that there be no difference in the use of antipyretic strategies (e.g., with acetaminophen or NSAIDs) between patients with or without COVID-19 (**AIII**).

In mid-March 2020, news agencies promoted reports that anti-inflammatory drugs may worsen COVID-19. It has been proposed that NSAIDs such as ibuprofen can increase the expression of ACE2¹ and inhibit antibody production.¹³ Shortly after these reports, the Food and Drug Administration stated that there is no evidence linking the use of NSAIDs with worsening of COVID-19 and advised patients to use NSAIDs as directed.¹⁴

References

1. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med*. 2020;8(4):e21. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32171062>.
2. Patel AB, Verma A. COVID-19 and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: what is the evidence? *JAMA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32208485>.
3. American College of Cardiology. HFSA/ACC/AHA statement addresses concerns re: using RAAS antagonists in COVID-19. 2020. Available at: <https://www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statement-addresses-concerns-re-using-raas-antagonists-in-covid-19>. Accessed July 16, 2020.
4. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. *J Heart Lung Transplant*. 2020;39(5):405-407. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32362390>.
5. Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid therapy for critically ill patients with Middle East respiratory syndrome. *Am J Respir Crit Care Med*. 2018;197(6):757-767. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29161116>.
6. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Med*. 2006;3(9):e343. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16968120>.
7. Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, Lim WS. Corticosteroids as adjunctive therapy in the treatment of influenza. *Cochrane Database Syst Rev*. 2016;3:CD010406. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26950335>.
8. Horby P, Lim WS, Emberson J, et al. Effect of dexamethasone in hospitalized patients with COVID-19: preliminary report. *medRxiv*. 2020:[Preprint]. Available at: <https://www.medrxiv.org/content/10.1101/2020.06.22.20137273v1>.
9. Kaiser UB, Mirmira RG, Stewart PM. Our response to COVID-19 as endocrinologists and diabetologists. *J Clin Endocrinol Metab*. 2020;105(5). Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32232480>.
10. Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. *Pediatrics*. 1972;50(4):515-525. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/4561295>.
11. Gyamfi-Bannerman C, Thom EA, Blackwell SC, et al. Antenatal betamethasone for women at risk for late preterm delivery. *N Engl J Med*. 2016;374(14):1311-1320. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26842679>.
12. Fedson DS, Opal SM, Rordam OM. Hiding in plain sight: an approach to treating patients with severe COVID-19 infection. *mBio*. 2020;11(2). Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32198163>.
13. Bancos S, Bernard MP, Topham DJ, Phipps RP. Ibuprofen and other widely used non-steroidal anti-inflammatory drugs inhibit antibody production in human cells. *Cell Immunol*. 2009;258(1):18-28. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19345936>.
14. Food and Drug Administration. FDA advises patients on use of non-steroidal anti-inflammatory drugs (NSAIDs) for COVID-19. 2020. <https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-patients-use-non-steroidal-anti-inflammatory-drugs-nsaids-covid-19>. Accessed July 16, 2020.

COVID-19 and Special Populations

Last Updated: October 9, 2020

To date, most of the data generated about the epidemiology, clinical course, prevention, and treatment of COVID-19 have come from studies of nonpregnant adults. More information is urgently needed regarding COVID-19 in other patient populations, such as in children, pregnant individuals, and other populations as outlined in the following sections of the Guidelines.

Although children with COVID-19 may have less severe disease overall than adults with COVID-19, the recently described multisystem inflammatory syndrome in children (MIS-C) requires further study. Data are also emerging on the clinical course of COVID-19 in pregnant patients, pregnancy outcomes in the setting of COVID-19, and vertical transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). There are special considerations for transplant recipients, patients with cancer, persons with HIV, and patients with other immunocompromising conditions, as some of these patients may be at increased risk of serious complications as a result of COVID-19.

The following sections review the available data on COVID-19 in some of these populations and discuss the specific considerations that clinicians should take into account for the prevention and treatment of SARS-CoV-2 infections in these populations.

Special Considerations in Pregnancy

Last Updated: August 27, 2020

Key Considerations

There is current guidance from the [Centers for Disease Control and Prevention \(CDC\)](#), the [American College of Obstetricians and Gynecologists \(ACOG\)](#), and the [Society for Maternal-Fetal Medicine \(SMFM\)](#) on the management of pregnant patients with COVID-19.¹⁻⁴ This section of the COVID-19 Treatment Guidelines complements that guidance. Below are key considerations regarding the management of COVID-19 in pregnancy.

- Pregnant women should be counseled about the potential for severe disease from SARS-CoV-2 infection and the recommended measures to take to protect themselves and their families from infection.
- If hospitalization for COVID-19 is indicated in a pregnant woman, care should be provided in a facility that can conduct maternal and fetal monitoring, when appropriate.
- Management of COVID-19 in the pregnant patient should include:
 - Fetal and uterine contraction monitoring, when appropriate, based on gestational age
 - Individualized delivery planning
 - A multispecialty, team-based approach that may include consultation with obstetric, maternal-fetal medicine, infectious disease, pulmonary and critical care, and pediatric specialists, as appropriate
- The COVID-19 Treatment Guidelines Panel (the Panel) recommends that potentially effective treatment for COVID-19 should not be withheld from pregnant women because of theoretical concerns related to the safety of therapeutic agents in pregnancy (**AIII**).
- Decisions regarding the use of drugs approved for other indications or investigational drugs for the treatment of COVID-19 in pregnant patients must be made with shared decision-making between the patient and the clinical team, considering the safety of the medication for the pregnant woman and the fetus and the severity of maternal disease. For detailed guidance on the use of COVID-19 therapeutic agents in pregnancy, please refer to the pregnancy considerations subsection of each individual section of the Guidelines.

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

Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

Epidemiology of COVID-19 in Pregnancy

Initial reports of COVID-19 disease acquired in the third trimester were reassuring, although most early data were limited to case reports and case series.⁵⁻⁷ Since that time, a large population-based cohort study in the United Kingdom evaluated outcomes in pregnant women hospitalized with confirmed severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infection. Among 427 pregnant women admitted to 197 obstetric units across the United Kingdom, the rates of critical care admission and severe SARS-CoV-2-associated maternal mortality were similar to those in the general population of women of reproductive age hospitalized with COVID-19 in the United Kingdom, although the pregnant women were not compared with age-matched, nonpregnant controls.⁸

In June 2020, the Centers for Disease Control and Prevention (CDC) released surveillance data evaluating SARS-CoV-2-related outcomes in reproductive aged women by pregnancy status. Among 326,335 women aged 15 to 44 years with positive test results for SARS-CoV-2, pregnant women were more likely to be hospitalized, be admitted to an intensive care unit (ICU), and receive mechanical ventilation. However, the overall absolute increase in rates of ICU admission and mechanical ventilation was low among the pregnant women and the nonpregnant women (1.5% vs. 0.9% for ICU admission, respectively, and 0.5% vs 0.3% for mechanical ventilation, respectively). COVID-19-related death rates were similar in the pregnant and nonpregnant populations. Pregnancy outcomes such as preterm birth or pregnancy loss were not evaluated.

This analysis has a number of significant limitations, including:

- Pregnancy status was only available for 28% of the women of reproductive age with SARS-CoV-2 infection.
- It was not possible to determine whether the reasons for hospitalization, ICU admission, or mechanical ventilation were related to COVID-19, pregnancy, and/or delivery.

Pregnant women who are Hispanic or Black may be disproportionately affected by SARS-CoV-2 infection.⁹ Pregnant women should be counseled about the potential for severe disease from SARS-CoV-2 and measures to protect themselves and their families from infection, including physical distancing, face coverings, and hand hygiene. CDC, ACOG, and SMFM highlight the importance of accessing prenatal care. ACOG provides an [FAQ](#) on using telehealth to deliver antenatal care, when appropriate.

ACOG has developed an [algorithm](#) to evaluate and manage pregnant outpatients with suspected or confirmed SARS-CoV-2 infection. As in nonpregnant patients, SARS-CoV-2 infection in pregnant patients can present as asymptomatic/presymptomatic disease or with a wide range of clinical manifestations, from mild symptoms that can be managed with supportive care at home to severe disease and respiratory failure requiring ICU admission. As with other patients, in the pregnant patient with symptoms compatible with COVID-19, the illness severity, underlying comorbidities, and clinical status should all be assessed to determine whether in-person evaluation for potential hospitalization is needed.

If hospitalization is indicated, care should be provided in a facility that can conduct maternal and fetal monitoring, when appropriate. The management of COVID-19 in the pregnant patient may include:

- Fetal and uterine contraction monitoring, when appropriate, based on gestational age
- Individualized delivery planning
- A multispecialty, team-based approach that may include consultation with obstetric, maternal-fetal medicine, infectious disease, pulmonary and critical care, and pediatric specialists, as appropriate.

Other recommendations on the management of COVID-19, as outlined for the nonpregnant patient, also apply in pregnancy.

Timing of Delivery

- Detailed guidance relating to timing of delivery and risk of vertical transmission of SARS-CoV-2 is provided by ACOG.¹⁰
- In most cases, the timing of delivery should be dictated by obstetric indications rather than maternal diagnosis of COVID-19. For women who had suspected or confirmed COVID-19 early in pregnancy who recover, no alteration to the usual timing of delivery is indicated.
- Vertical transmission of SARS-CoV-2 via the transplacental route appears to be rare but possible.¹¹⁻¹³

Management of COVID-19 in the Setting of Pregnancy

- Potentially effective treatment for COVID-19 should not be withheld from pregnant women because of theoretical concerns related to the safety of therapeutic agents in pregnancy (**AIII**).
- Decisions regarding the use of drugs approved for other indications or investigational agents for the treatment of COVID-19 in pregnant patients must be made with shared decision-making between the patient and the clinical team, considering the safety of the medication for the woman

and the fetus and the severity of maternal disease. For detailed guidance on the use of COVID-19 therapeutic agents in pregnancy, please refer to the pregnancy considerations subsection of each individual section of the Guidelines.

- To date, most SARS-CoV-2-related clinical trials have excluded, or included only a very few, pregnant women and lactating women. This limitation makes it difficult to make evidence-based recommendations on the use of SARS-CoV-2 therapies in these vulnerable patients and potentially limits their COVID-19 treatment options. When possible, pregnant women and lactating women should not be excluded from clinical trials of therapeutic agents or vaccines for SARS-CoV-2 infection.

Post-Delivery

- Specific guidance for post-delivery management of infants born to mothers with known or suspected SARS-CoV-2 infection, including breastfeeding recommendations, is provided by the CDC^{14,15} and the [American Academy of Pediatrics](#).¹⁶

References

1. Centers for Disease Control and Prevention. Considerations for inpatient obstetric healthcare settings. 2020. Available at: <https://www.cdc.gov/coronavirus/2019-ncov/hcp/inpatient-obstetric-healthcare-guidance.html>. Accessed August 26, 2020.
2. The American College of Obstetricians and Gynecologists. Novel coronavirus 2019 (COVID-19): practice advisory. August 2020. Available at: <https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2020/03/novel-coronavirus-2019>. Accessed August 26, 2020.
3. Society for Maternal-Fetal Medicine. Coronavirus (COVID-19) and Pregnancy: What Maternal Fetal Medicine Subspecialists Need to Know. July 2020. [https://s3.amazonaws.com/cdn.smfm.org/media/2468/COVID19-What_MFMs_need_to_know_revision_7-23-20_\(final\).PDF](https://s3.amazonaws.com/cdn.smfm.org/media/2468/COVID19-What_MFMs_need_to_know_revision_7-23-20_(final).PDF). Accessed August 26, 2020.
4. Rasmussen SA, Smulian JC, Lednický JA, Wen TS, Jamieson DJ. Coronavirus disease 2019 (COVID-19) and pregnancy: what obstetricians need to know. *Am J Obstet Gynecol*. 2020;222(5):415-426. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32105680>.
5. Chen H, Guo J, Wang C, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet*. 2020;395(10226):809-815. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32151335>.
6. Liu Y, Chen H, Tang K, Guo Y. Clinical manifestations and outcome of SARS-CoV-2 infection during pregnancy. *J Infect*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32145216>.
7. World Health Organization. Report of the WHO-China joint mission on coronavirus disease 2019 (COVID-19). 2020. Available at: <https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf>. Accessed August 26, 2020.
8. Knight M, Bunch K, Vousden N, et al. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study. *BMJ*. 2020;369:m2107. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32513659>.
9. Ellington S, Strid P, Tong VT, et al. Characteristics of women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status—United States, January 22-June 7, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(25):769-775. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32584795>.
10. The American College of Obstetricians and Gynecologists. COVID-19 FAQs for Obstetricians-Gynecologists, Obstetrics. 2020. Available at: <https://www.acog.org/clinical-information/physician-faqs/covid-19-faqs-for-ob-gyns-obstetrics>. Accessed August 26, 2020.
11. Thomas P, Alexander PE, Ahmed U, et al. Vertical transmission risk of SARS-CoV-2 infection in the third trimester: a systematic scoping review. *J Matern Fetal Neonatal Med*. 2020:1-8. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/32611247>.

12. Matar R, Alrahmani L, Monzer N, et al. Clinical presentation and outcomes of pregnant women with COVID-19: a systematic review and meta-analysis. *Clin Infect Dis*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32575114>.
13. Vivanti AJ, Vauloup-Fellous C, Prevot S, et al. Transplacental transmission of SARS-CoV-2 infection. *Nat Commun*. 2020;11(1):3572. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32665677>.
14. Centers for Disease Control and Prevention. Evaluation and management considerations for neonates at risk for COVID-19. 2020. <https://www.cdc.gov/coronavirus/2019-ncov/hcp/caring-for-newborns.html>. Accessed August 26, 2020.
15. Centers for Disease Control and Prevention. Care for breastfeeding women: interim guidance on breastfeeding and breast milk feeds in the context of COVID-19. 2020. Available at: <https://www.cdc.gov/coronavirus/2019-ncov/hcp/care-for-breastfeeding-women.html>. Accessed August 26, 2020.
16. American Academy of Pediatrics. FAQs: management of infants born to mothers with suspected or confirmed COVID-19. 2020. Available at: <https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/faqs-management-of-infants-born-to-covid-19-mothers/>. Accessed August 26, 2020.

Special Considerations in Children

Last Updated: November 3, 2020

Data on disease severity and pathogenesis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children are limited. Overall, several large epidemiologic studies suggest that acute disease manifestations are substantially less severe in children than in adults, although there are reports of children with COVID-19 requiring intensive care unit (ICU)-level care.¹⁻¹¹ Recently, SARS-CoV-2 has been associated with a potentially severe inflammatory syndrome in children (multisystem inflammatory syndrome in children [MIS-C], which is discussed below). Preliminary data from the Centers for Disease Control and Prevention (CDC) also show that hospitalization rates and ICU admission rates for children are lower than for adults. Severe cases of COVID-19 in children were associated with younger age and underlying conditions, although a significant number of the pediatric cases did not have complete data available at the time of the preliminary report. Without widespread testing, including for mild symptoms, the true incidence of severe disease in children is unclear. Data on perinatal vertical transmission to neonates are limited to small case series with conflicting results; some studies have demonstrated lack of transmission, whereas others have not been able to definitively rule out this possibility.¹²⁻¹⁴ Specific guidance on the diagnosis and management of COVID-19 in neonates born to mothers with known or suspected SARS-CoV-2 infection is provided by the [CDC](#).

Insufficient data are available to clearly establish risk factors for severe COVID-19 disease in children. Based on adult data and extrapolation from other pediatric respiratory viruses, severely immunocompromised children and those with underlying cardiopulmonary disease may be at higher risk for severe disease. Children with risk factors recognized in adults, including obesity, diabetes, and hypertension, may also be at risk, although there are no published data supporting this association and insufficient data to guide therapy. Guidance endorsed by the Pediatric Infectious Diseases Society has recently been published, which provides additional specific risk categorization when considering therapy.¹⁵ As data emerge on risk factors for severe disease, it may be possible to provide more directed guidance for specific populations at high risk for COVID-19 and to tailor treatment recommendations accordingly.

Currently, remdesivir is the only drug approved by the Food and Drug Administration (FDA) for the treatment of COVID-19 in hospitalized patients (see [Remdesivir](#) for detailed information). It is approved for children with COVID-19 who are aged ≥ 12 years and weigh ≥ 40 kg. Remdesivir is also available for younger children (and those weighing < 40 kg and > 3.5 kg) through an FDA Emergency Use Authorization.

For other agents outlined in these guidelines, there are insufficient data to recommend for or against the use of specific antivirals or immunomodulatory agents for the treatment of COVID-19 in pediatric patients. General considerations such as underlying conditions, disease severity, and potential for drug toxicity or drug interactions may inform management decisions on a case-by-case basis. Enrollment of children in clinical trials should be prioritized when trials are available. A number of additional drugs are being investigated for the treatment of COVID-19 in adults; clinicians can refer to the considerations in children subsection of each individual section of the Guidelines for more information on using these drugs in children.

Multisystem Inflammatory Syndrome in Children

Emerging reports from Europe and the United States have suggested that COVID-19 may be associated with MIS-C (also referred to as pediatric multisystem inflammatory syndrome—temporally associated with SARS-CoV-2 [PMIS-TS]). The syndrome was first described in the United Kingdom, where previously healthy children with severe inflammation and Kawasaki disease-like features were identified

to have current or recent infection with SARS-CoV-2.^{16,17} Additional cases of MIS-C have been reported in other European countries, including Italy and France.^{18,19} Emerging data suggest that MIS-C may be associated with pediatric patients who are slightly older than children typically seen with Kawasaki disease, and some cases of MIS-C in young adults have been reported.

In the United States, from April 16 through May 4, 2020, the New York City Department of Health and Mental Hygiene received reports of 15 hospitalized children with clinical presentation consistent with MIS-C. Subsequently, the New York State Department of Health has been investigating several hundred cases and a few deaths in children with similar presentations, many of whom tested positive for SARS-CoV-2 infection by reverse transcriptase polymerase chain reaction (PCR) or serology.²⁰ Several other states are now reporting cases consistent with MIS-C.

The current case definition for MIS-C can be found on the [CDC website](#). This case definition, which may evolve as more data become available, includes:

- Fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multiorgan involvement, *and*
- No alternate diagnosis, *and*
- Recent or current SARS-CoV-2 infection or exposure to COVID-19.

From the available data, patients with MIS-C present with persistent fever, evidence of systemic inflammation, and a variety of signs and symptoms of multiorgan system involvement, including cardiac, gastrointestinal, renal, hematologic, dermatologic, and neurologic involvement.

Some patients who meet criteria for MIS-C also meet criteria for complete or incomplete Kawasaki disease. An observational study compared data from Italian children with Kawasaki-like illness that was diagnosed before and after the onset of the SARS-CoV-2 epidemic. The data suggest that the SARS-CoV-2-associated cases occurred in children who were older than the children with Kawasaki-like illness diagnosed prior to the COVID-19 epidemic. In addition, the rates of cardiac involvement, associated shock, macrophage activation syndrome, and need for adjunctive steroid treatment were higher for the SARS-CoV-2-associated cases.¹⁸ Many patients with MIS-C have abnormal markers of cardiac injury or dysfunction, including troponin and brain natriuretic protein. Echocardiographic findings include impaired left ventricular function, as well as coronary artery dilations, and rarely, coronary artery aneurysms. At presentation, few patients are SARS-CoV-2 PCR positive (nasopharyngeal or nasal swab or stool sample), but most have detectable antibodies to SARS-CoV-2. Emerging observations suggest that there may be a wider range of severity of symptoms than initially recognized. Epidemiologic and clinical data suggest that MIS-C may represent a post-infectious inflammatory phenomenon rather than a direct viral process. The role of asymptomatic infection and the pattern of timing between SARS-CoV-2 infection and MIS-C are not well understood, and currently a causal relationship is not established.

Currently, there is limited information available about risk factors, pathogenesis, clinical course, and treatment for MIS-C. Supportive care remains the mainstay of therapy. There are currently insufficient data for the COVID-19 Treatment Guidelines Panel to recommend either for or against any therapeutic strategy for the management of MIS-C. Although no definitive data are available, many centers consider the use of intravenous immune globulin, steroids, and other immunomodulators (including interleukin-1 and interleukin-6 inhibitors) for therapy, and antiplatelet and anticoagulant therapy. The role of antiviral medications that specifically target SARS-CoV-2 is not clear at this time. MIS-C management decisions should involve a multidisciplinary team of pediatric specialists in intensive care, infectious diseases, cardiology, hematology, and rheumatology.

References

1. Sun D, Li H, Lu XX, et al. Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center's observational study. *World J Pediatr*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32193831>.
2. Cui Y, Tian M, Huang D, et al. A 55-day-old female infant infected with COVID 19: presenting with pneumonia, liver injury, and heart damage. *J Infect Dis*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32179908>.
3. Cai J, Xu J, Lin D, et al. A Case Series of children with 2019 novel coronavirus infection: clinical and epidemiological features. *Clin Infect Dis*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32112072>.
4. Kam KQ, Yung CF, Cui L, et al. A well infant with coronavirus disease 2019 (COVID-19) with high viral load. *Clin Infect Dis*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32112082>.
5. Dong Y, Mo X, Hu Y, et al. Epidemiological characteristics of 2,143 pediatric patients with 2019 coronavirus disease in China. *Pediatrics*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32179660>.
6. Centers for Disease Control and Prevention. Coronavirus Disease 2019 in Children—United States, February 12–April 2, 2020. 2020. Available at: <https://www.cdc.gov/mmwr/volumes/69/wr/mm6914e4.htm>. Accessed June 5, 2020.
7. Cui X, Zhang T, Zheng J, et al. Children with coronavirus disease 2019 (covid-19): a review of demographic, clinical, laboratory and imaging features in 2,597 pediatric patients. *J Med Virol*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32418216>.
8. Livingston E, Bucher K. Coronavirus Disease 2019 (COVID-19) in Italy. *JAMA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32181795>.
9. Tagarro A, Epalza C, Santos M, et al. Screening and severity of coronavirus disease 2019 (COVID-19) in children in Madrid, Spain. *JAMA Pediatr*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32267485>.
10. DeBiasi RL, Song X, Delaney M, et al. Severe COVID-19 in children and young adults in the Washington, DC metropolitan region. *J Pediatr*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32405091>.
11. Chao JY, Derespina KR, Herold BC, et al. Clinical characteristics and outcomes of hospitalized and critically ill children and adolescents with coronavirus disease 2019 (COVID-19) at a Tertiary Care Medical Center in New York City. *J Pediatr*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32407719>.
12. Chen H, Guo J, Wang C, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet*. 2020;395(10226):809-815. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32151335>.
13. Fan C, Lei D, Fang C, et al. Perinatal transmission of COVID-19 associated SARS-CoV-2: should we worry? *Clin Infect Dis*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32182347>.
14. Zeng L, Xia S, Yuan W, et al. Neonatal early-onset infection with SARS-CoV-2 in 33 neonates born to mothers with COVID-19 in Wuhan, China. *JAMA Pediatr*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32215598>.
15. Chiotos K, Hayes M, Kimberlin DW, et al. Multicenter initial guidance on use of antivirals for children with COVID-19/SARS-CoV-2. *J Pediatric Infect Dis Soc*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32318706>.
16. Royal College of Paediatrics and Child Health. Guidance: Paediatric multisystem inflammatory syndrome temporally associated with COVID-19. 2020. Available at: <https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf>. Accessed May 28, 2020.
17. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet*. 2020;395(10237):1607-1608. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32386565>.
18. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet*. 2020. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/32410760>.

19. Toubiana J, Poirault C, Corsia A, et al. Outbreak of Kawasaki disease in children during COVID-19 pandemic: a prospective observational study in Paris, France. *medRxiv*. 2020:[Preprint]. Available at: <https://www.medrxiv.org/content/10.1101/2020.05.10.20097394v1>.
20. New York State. Childhood inflammatory disease related to COVID-19. 2020; <https://coronavirus.health.ny.gov/childhood-inflammatory-disease-related-covid-19>. Accessed June 1, 2020.

Special Considerations in Adults and Children With Cancer

Last Updated: August 27, 2020

Summary Recommendations
<ul style="list-style-type: none">• The COVID-19 Treatment Guidelines Panel recommends molecular diagnostic testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in patients with cancer who develop signs and symptoms that suggest COVID-19 (AIII) and in asymptomatic patients prior to procedures that require anesthesia and before initiating cytotoxic chemotherapy and long-acting biologic therapy (BIII).• The recommendations for treating COVID-19 in patients with cancer are the same as those for the general population (AIII) (see Potential Antiviral Drugs Under Evaluation for the Treatment of COVID-19 and Immunomodulators Under Evaluation for the Treatment of COVID-19).• Clinicians should pay careful attention to potential drug-drug interactions and overlapping toxicities between drugs that are used to treat COVID-19 and cancer-directed therapies, prophylactic antimicrobials, corticosteroids, and other medications (AIII).• Clinicians who are treating COVID-19 in patients with cancer should consult with a hematologist or oncologist before adjusting cancer-directed medications (AIII).• Decisions about administering cancer-directed therapy during SARS-CoV-2 infection should be made on a case-by-case basis; clinicians should consider the indication for chemotherapy, the goals of care, and the patient's history of tolerance to the treatment (BIII).
Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

People who are being treated for cancer may be at increased risk of severe COVID-19, and their outcomes are worse than individuals without cancer.¹⁻⁴ A meta-analysis of 46,499 patients with COVID-19 showed that all-cause mortality (risk ratio 1.66; 95% CI, 1.33–2.07) was higher in patients with cancer, and that patients with cancer were more likely to be admitted to intensive care units (risk ratio 1.56; 95% CI, 1.31–1.87).⁵ The risk for immunosuppression and susceptibility to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection varies between cancer types, treatments administered, and stages of therapy (e.g., patients who are actively being treated compared to those in remission). In a study that used data from the COVID-19 and Cancer Consortium Registry, cancer patients who were in remission or who had no evidence of disease were at a lower risk of death from COVID-19 than those who were receiving active treatment.⁶ It is unclear whether cancer survivors are at increased risk for severe COVID-19 and its complications compared to people without a history of cancer.

Many organizations have outlined recommendations for treating patients with cancer during the COVID-19 pandemic, such as:

- [National Comprehensive Cancer Network \(NCCN\)](#)
- [American Society of Hematology](#)
- [American Society of Clinical Oncology](#)
- [Society of Surgical Oncology](#)
- [American Society for Radiation Oncology](#)
- [International Lymphoma Radiation Oncology Group](#)

This section of the COVID-19 Treatment Guidelines complements these sources and focuses on considerations regarding testing for SARS-CoV-2, management of COVID-19 in patients with cancer, and management of cancer-directed therapies during the COVID-19 pandemic. The optimal

management and therapeutic approach to COVID-19 in this population has not yet been defined.

Testing for COVID-19 in Patients With Cancer

The COVID-19 Treatment Guidelines Panel (the Panel) recommends molecular diagnostic testing for SARS-CoV-2 in patients with cancer who develop signs and symptoms of COVID-19 (**AIII**).

Patients with cancer who are receiving chemotherapy are at risk of developing neutropenia. The NCCN [*Guidelines for Hematopoietic Growth Factors*](#) categorizes cancer treatment regimens based on the risk of developing neutropenia. A retrospective study suggests that cancer patients with neutropenia have a higher mortality rate if they develop COVID-19.⁷ Due to the potential risk of poor clinical outcomes in the setting of neutropenia and/or during the perioperative period, the Panel recommends performing molecular diagnostic testing for SARS-CoV-2 prior to procedures that require anesthesia and before initiating cytotoxic chemotherapy and long-acting biologic therapy (**BIII**).^{8,9}

General Guidance on Medical Care for Cancer Patients During the COVID-19 Pandemic

Patients with cancer frequently engage with the health care system to receive treatment and supportive care for cancer and/or treatment-related complications. Telemedicine can minimize the need for in-person services and reduce the risk of SARS-CoV-2 exposure. The Centers for Disease Control and Prevention published a framework to help clinicians decide whether a patient should receive in-person or virtual care during the COVID-19 pandemic; this framework accounts for factors such as the potential harm of delayed care and the degree of SARS-CoV-2 transmission in a patient's community.¹⁰ Telemedicine may improve access to providers for medically or socially vulnerable populations but could worsen disparities if these populations have limited access to technology. Nosocomial transmission of SARS-CoV-2 to patients and health care workers has been reported.¹¹⁻¹³ Principles of physical distancing and prevention strategies, including masking patients and health care workers and practicing hand hygiene, apply to all in-person interactions.¹⁴

Decisions about treatment regimens, surgery, and radiation therapy for the underlying malignancy should be made on an individual basis depending on the biology of the cancer, the need for hospitalization, the number of clinic visits required, and the anticipated degree of immunosuppression. Several key points should be considered:

- If possible, treatment delays should be avoided for curable cancers that have been shown to have worse outcomes when treatment is delayed (e.g., pediatric acute lymphoblastic leukemia).
- When deciding between equally effective treatment regimens, regimens that can be administered orally or those that require fewer infusions are preferred.^{15,16}
- The potential risks of drug-related lung toxicity (e.g., from using bleomycin or PD1 inhibitors) must be balanced with the clinical efficacy of alternative regimens or the risk of delaying care.¹⁷
- Preventing neutropenia can decrease the risk of neutropenic fever and the need for emergency room evaluation and hospitalization during the COVID-19 pandemic. Granulocyte colony-stimulating factor (G-CSF) should be given with chemotherapy regimens that have intermediate (10% to 20%) or high (>20%) risks of febrile neutropenia.¹⁸
- Cancer treatment regimens that do not affect outcomes of COVID-19 in cancer patients may not need to be altered. In a prospective observational study, receipt of immunotherapy, hormonal therapy, or radiotherapy in the month prior to SARS-CoV-2 infection was not associated with an increased risk of mortality among cancer patients with COVID-19.¹⁹ A retrospective study from Italy evaluated the incidence of SARS-CoV-2 infection in patients with prostate cancer and

found that 114 of 37,161 patients (0.3%) who were treated with therapies other than androgen deprivation therapy became infected, compared to four of 5,273 patients (0.08%) who were treated with androgen deprivation therapy (OR 4.05; 95% CI, 1.55–10.59). The viral spike proteins required for cell entry of SARS-CoV-2 are primed by TMPRSS2, an androgen-regulated gene. Whether androgen deprivation therapy protects against SARS-CoV-2 infection requires further investigation in larger cohorts.²⁰

- Radiation therapy guidelines suggest increasing the dose per fraction and reducing the number of daily treatments in order to minimize the number of hospital visits during the COVID-19 pandemic.^{15,16}

Blood supply shortages will likely continue during the COVID-19 pandemic due to social distancing, cancellation of blood drives, and infection among donors. Revised donor criteria have been proposed by the Food and Drug Administration to increase the number of eligible donors.²¹ In patients with cancer, lowering the transfusion thresholds for blood products (e.g., red blood cells, platelets) in asymptomatic patients should be considered.^{22,23} At this time, there is no evidence that COVID-19 can be transmitted through blood products.^{24,25}

Febrile Neutropenia

Cancer patients with febrile neutropenia should undergo molecular diagnostic testing for SARS-CoV-2 and evaluation for other infectious agents; they should also be given empiric antibiotics, as outlined in the NCCN Guidelines.²⁶ Low-risk febrile neutropenia patients should be treated at home with oral antibiotics or intravenous infusions of antibiotics to limit nosocomial exposure to SARS-CoV-2. Patients with high-risk febrile neutropenia should be hospitalized per standard of care.²⁶ Empiric antibiotics should be continued per standard of care in patients who test positive for SARS-CoV-2. Clinicians should also continuously evaluate neutropenic patients for emergent infections.

Treating COVID-19 and Managing Chemotherapy in Patients With Cancer and COVID-19

Retrospective studies suggest that patients with cancer who were admitted to the hospital with SARS-CoV-2 infection have a high case fatality rate, with higher rates observed in patients with hematologic malignancies than in those with solid tumors.^{27,28}

Recommendations for treatment of COVID-19 are the same for cancer patients as for the general population (**AIII**) (see [Potential Antiviral Drugs Under Evaluation for the Treatment of COVID-19](#) and [Immunomodulators Under Evaluation for the Treatment of COVID-19](#)). Dexamethasone treatment in patients with COVID-19 who require supplemental oxygen or mechanical ventilation has been associated with a lower mortality rate.²⁹ In cancer patients, dexamethasone is commonly used to prevent chemotherapy-induced nausea, as a part of tumor-directed therapy, and to treat inflammation associated with brain metastasis. The side effects of using dexamethasone to treat SARS-CoV-2 are not anticipated to be different between patients with or without cancer. If possible, treatments that are not currently recommended for SARS-CoV-2 infection should be administered as part of a clinical trial, since the safety and efficacy of these agents have not been well defined in patients with cancer.

The NCCN recommends discontinuing G-CSF and granulocyte-macrophage colony-stimulating factor in patients with cancer and acute SARS-CoV-2 infection who do not have bacterial or fungal infections to avoid the hypothetical risk of increasing inflammatory cytokines and pulmonary inflammation.^{18,30} Secondary infections (e.g., invasive pulmonary aspergillosis) have been reported in critically ill patients with COVID-19.^{31,32}

Decisions about administering cancer-directed therapy to patients with acute COVID-19 and those who are recovering from COVID-19 should be made on a case-by-case basis; clinicians should consider the indication for chemotherapy, the goals of care, and the patient's history of tolerance to the treatment **(BIII)**. The optimal duration of time between resolution of infection and initiating or restarting cancer-directed therapy is unclear. Withholding treatment until COVID-19 symptoms have resolved is recommended, if possible. Prolonged viral shedding (detection of SARS-CoV-2 by molecular testing) may occur in cancer patients,² although it is unknown how this relates to infectious virus and how it impacts outcomes. Therefore, there is no role for repeat testing in those recovering from COVID-19, and the decision to restart cancer treatments in this setting should be made on a case-by-case basis. The Panel recommends that clinicians who are treating COVID-19 in patients with cancer consult with a hematologist or oncologist before adjusting cancer-directed medications **(AIII)**.

Medication Interactions

The use of potential antiviral or immune-based therapies to treat COVID-19 can present additional challenges in cancer patients. Clinicians should pay careful attention to potential drug-drug interactions and overlapping toxicities between drugs that are used to treat COVID-19 and cancer-directed therapies, prophylactic antimicrobials, corticosteroids, and other medications **(AIII)**.

Several anti-neoplastic medications have known interactions with therapies that are being investigated for COVID-19.²² Tocilizumab can interact with vincristine and doxorubicin. Any COVID-19 therapy that may cause QT prolongation must be used with caution in patients treated with venetoclax, gilteritinib, and tyrosine kinase inhibitor therapy (e.g., nilotinib). Dexamethasone is commonly used as an antiemetic for cancer patients and is recommended for treatment of certain patients with COVID-19 (see [Corticosteroids](#) for more information). Dexamethasone is a weak to moderate cytochrome P450 (CYP) 3A4 inducer; therefore, interactions with any CYP3A4 substrates need to be considered. Lopinavir/ritonavir is a CYP3A4 inhibitor, and it can increase methotrexate, vincristine, or ruxolitinib concentrations. Lopinavir/ritonavir **is not recommended** for the treatment of COVID-19; however, patients may receive it in a clinical trial. In general, concomitant use of lopinavir/ritonavir and CYP3A4 substrates should be avoided. If lopinavir/ritonavir is used in combination with a cytotoxic drug that is also a CYP3A4 substrate, clinicians should monitor for toxicities of the cytotoxic drug and adjust the dose if necessary.

Special Considerations in Children

Preliminary published reports suggest that pediatric patients with cancer may have milder manifestations of COVID-19 than adult patients with cancer, although larger studies are needed.³³⁻³⁵ Guidance on managing children with cancer during the COVID-19 pandemic is available from an international group with input from the International Society of Paediatric Oncology, the Children's Oncology Group, St. Jude Global, and Childhood Cancer International.³⁶ Two publications include guidance for managing specific malignancies, guidance for supportive care, and a summary of web links from expert groups that are relevant to the care of pediatric oncology patients during the COVID-19 pandemic.^{36,37} Special considerations for using antivirals in immunocompromised children, including those with malignancy, are available in a multicenter guidance statement.³⁸

References

1. Dai M, Liu D, Liu M, et al. Patients with cancer appear more vulnerable to SARS-CoV-2: a multicenter study during the COVID-19 outbreak. *Cancer Discov*. 2020;10(6):783-791. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32345594>.
2. Shah V, Ko Ko T, Zuckerman M, et al. Poor outcome and prolonged persistence of SARS-CoV-2 RNA in

- COVID-19 patients with haematological malignancies; King's College Hospital experience. *Br J Haematol*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32526039>.
3. Yang K, Sheng Y, Huang C, et al. Clinical characteristics, outcomes, and risk factors for mortality in patients with cancer and COVID-19 in Hubei, China: a multicentre, retrospective, cohort study. *Lancet Oncol*. 2020;21(7):904-913. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32479787>.
 4. Robilotti EV, Babady NE, Mead PA, et al. Determinants of COVID-19 disease severity in patients with cancer. *Nat Med*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32581323>.
 5. Giannakoulis VG, Papoutsis E, Siempos, II. Effect of cancer on clinical outcomes of patients with COVID-19: a meta-analysis of patient data. *JCO Glob Oncol*. 2020;6:799-808. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32511066>.
 6. Kuderer NM, Choueiri TK, Shah DP, et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. *Lancet*. 2020;395(10241):1907-1918. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32473681>.
 7. Yarza R, Bover M, Paredes D, et al. SARS-CoV-2 infection in cancer patients undergoing active treatment: analysis of clinical features and predictive factors for severe respiratory failure and death. *Eur J Cancer*. 2020;135:242-250. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32586724>.
 8. American Society of Clinical Oncology. ASCO Special Report: A guide to cancer care delivery during the COVID-19 pandemic. 2020. Available at: <https://www.asco.org/sites/new-www.asco.org/files/content-files/2020-ASCO-Guide-Cancer-COVID19.pdf>. Accessed August 17, 2020.
 9. American Society of Anesthesiologists. The ASA and APSF joint statement on perioperative testing for the COVID-19 virus. 2020. Available at: <https://www.asahq.org/about-asa/newsroom/news-releases/2020/06/asa-and-apsf-joint-statement-on-perioperative-testing-for-the-covid-19-virus>. Accessed August 3, 2020.
 10. Centers for Disease Control and Prevention. Coronavirus Disease 2019 (COVID-19): framework for healthcare systems providing non-COVID-19 clinical care during the COVID-19 pandemic. 2020. Available at: <https://www.cdc.gov/coronavirus/2019-ncov/hcp/framework-non-COVID-care.html>. Accessed August 3, 2020.
 11. Wang X, Zhou Q, He Y, et al. Nosocomial outbreak of COVID-19 pneumonia in Wuhan, China. *Eur Respir J*. 2020;55(6). Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32366488>.
 12. Luong-Nguyen M, Hermand H, Abdalla S, et al. Nosocomial infection with SARS-CoV-2 within Departments of Digestive Surgery. *J Visc Surg*. 2020;157(3S1):S13-S18. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32381426>.
 13. Rivett L, Sridhar S, Sparkes D, et al. Screening of healthcare workers for SARS-CoV-2 highlights the role of asymptomatic carriage in COVID-19 transmission. *eLife*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32392129>.
 14. Centers for Disease Control and Prevention. Coronavirus Disease 2019 (COVID-19): how to protect yourself & others. 2020. Available at: <https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html>. Accessed June 17, 2020.
 15. American Society for Radiation Oncology. COVID-19 recommendations and information: COVID-19 clinical guidance. 2020. Available at: <https://www.astro.org/Daily-Practice/COVID-19-Recommendations-and-Information/Clinical-Guidance>. Accessed August 3, 2020.
 16. Yahalom J, Dabaja BS, Ricardi U, et al. ILROG emergency guidelines for radiation therapy of hematological malignancies during the COVID-19 pandemic. *Blood*. 2020;135(21):1829-1832. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32275740>.
 17. American Society of Hematology. COVID-19 and hodgkin lymphoma: frequently asked questions. 2020. Available at: <https://www.hematology.org/covid-19/covid-19-and-hodgkin-lymphoma>. Accessed August 3, 2020.

18. National Comprehensive Cancer Network. NCCN hematopoietic growth factors: short-term recommendations specific to issues with COVID-19 (SARS-CoV-2). 2020. Available at: https://www.nccn.org/covid-19/pdf/HGF_COVID-19.pdf. Accessed: August 3, 2020.
19. Lee LYW, Cazier JB, Starkey T, et al. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. *Lancet*. 2020;395(10241):1919-1926. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32473682>.
20. Montopoli M, Zumerle S, Vettor R, et al. Androgen-deprivation therapies for prostate cancer and risk of infection by SARS-CoV-2: a population-based study (N = 4532). *Ann Oncol*. 2020;31(8):1040-1045. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32387456>.
21. Food and Drug Administration. Coronavirus (COVID-19) update: FDA provides updated guidance to address the urgent need for blood during the pandemic. 2020. Available at: <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-provides-updated-guidance-address-urgent-need-blood-during-pandemic>. Accessed August 3, 2020.
22. American Society of Hematology. COVID-19 resources. 2020. Available at: <https://www.hematology.org/covid-19>. Accessed August 3, 2020.
23. American Society of Clinical Oncology. COVID-19 patient care information: cancer treatment & supportive care. 2020. Available at: <https://www.asco.org/asco-coronavirus-resources/care-individuals-cancer-during-covid-19/cancer-treatment-supportive-care>. Accessed August 3, 2020.
24. Food and Drug Administration. COVID-19 frequently asked questions. 2020. Available at: <https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-frequently-asked-questions>. Accessed August 3, 2020.
25. Centers for Disease Control and Prevention. Clinical questions about COVID-19: questions and answers. 2020. Available at: <https://www.cdc.gov/coronavirus/2019-ncov/hcp/faq.html#Transmission>. Accessed August 3, 2020.
26. National Comprehensive Cancer Network. Infectious disease management and considerations in cancer patients with documented or suspected COVID-19. 2020. Available at: https://www.nccn.org/covid-19/pdf/COVID_Infections.pdf. Accessed: August 3, 2020.
27. Mehta V, Goel S, Kabarriti R, et al. Case fatality rate of cancer patients with COVID-19 in a New York Hospital System. *Cancer Discov*. 2020;10(7):935-941. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32357994>.
28. Meng Y, Lu W, Guo E, et al. Cancer history is an independent risk factor for mortality in hospitalized COVID-19 patients: a propensity score-matched analysis. *J Hematol Oncol*. 2020;13(1):75. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32522278>.
29. Recovery Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with COVID-19—preliminary report. *N Engl J Med*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32678530>.
30. Nawar T, Morjaria S, Kaltsas A, et al. Granulocyte-colony stimulating factor in COVID-19: Is it stimulating more than just the bone marrow? *Am J Hematol*. 2020;95(8):E210-E213. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32419212>.
31. van Arkel ALE, Rijpstra TA, Belderbos HNA, van Wijngaarden P, Verweij PE, Bentvelsen RG. COVID-19-associated pulmonary aspergillosis. *Am J Respir Crit Care Med*. 2020;202(1):132-135. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32396381>.
32. Alanio A, Delliere S, Fodil S, Bretagne S, Megarbane B. Prevalence of putative invasive pulmonary aspergillosis in critically ill patients with COVID-19. *Lancet Respir Med*. 2020;8(6):e48-e49. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32445626>.
33. Hrusak O, Kalina T, Wolf J, et al. Flash survey on severe acute respiratory syndrome coronavirus-2 infections in paediatric patients on anticancer treatment. *Eur J Cancer*. 2020;132:11-16. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32305831>.

34. Andre N, Rouger-Gaudichon J, Brethon B, et al. COVID-19 in pediatric oncology from French pediatric oncology and hematology centers: High risk of severe forms? *Pediatr Blood Cancer*. 2020;67(7):e28392. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32383827>.
35. de Rojas T, Perez-Martinez A, Cela E, et al. COVID-19 infection in children and adolescents with cancer in Madrid. *Pediatr Blood Cancer*. 2020;67(7):e28397. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32383819>.
36. Sullivan M, Bouffet E, Rodriguez-Galindo C, et al. The COVID-19 pandemic: a rapid global response for children with cancer from SIOP, COG, SIOP-E, SIOP-PODC, IPSO, PROS, CCI, and St. Jude Global. *Pediatr Blood Cancer*. 2020;67(7):e28409. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32400924>.
37. Bouffet E, Challinor J, Sullivan M, Biondi A, Rodriguez-Galindo C, Pritchard-Jones K. Early advice on managing children with cancer during the COVID-19 pandemic and a call for sharing experiences. *Pediatr Blood Cancer*. 2020;67(7):e28327. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32239747>.
38. Chiotos K, Hayes M, Kimberlin DW, et al. Multicenter initial guidance on use of antivirals for children with COVID-19/SARS-CoV-2. *J Pediatric Infect Dis Soc*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32318706>.

Special Considerations in Solid Organ Transplant, Hematopoietic Stem Cell Transplant, and Cellular Therapy Candidates, Donors, and Recipients

Last Updated: November 3, 2020

Summary Recommendations
<p>Potential Transplant and Cellular Therapy Candidates</p> <ul style="list-style-type: none">• The COVID-19 Treatment Guidelines Panel (the Panel) recommends diagnostic molecular testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) for all potential solid organ transplant (SOT), hematopoietic cell transplant (HCT), and cell therapy candidates with signs and symptoms that suggest acute COVID-19 infection (AIII).• The Panel recommends following the guidance from medical professional organizations that specialize in providing care for SOT, HCT, or cell therapy recipients when performing diagnostic molecular testing for SARS-CoV-2 in these patients (AIII).• If SARS-CoV-2 is detected or if infection is strongly suspected, transplantation should be deferred, if possible (BIII). <p>Potential Transplant Donors</p> <ul style="list-style-type: none">• The Panel recommends assessing all potential SOT donors for signs and symptoms that are associated with COVID-19 according to guidance from medical professional organizations (AIII).<ul style="list-style-type: none">• The Panel recommends performing diagnostic molecular testing for SARS-CoV-2 if symptoms are present (AIII).• If SARS-CoV-2 is detected or if infection is strongly suspected, donation should be deferred (BIII).• The Panel recommends assessing all potential HCT donors for signs and symptoms that are associated with COVID-19 according to guidance from medical professional organizations (AIII).<ul style="list-style-type: none">• The Panel recommends performing diagnostic molecular testing for SARS-CoV-2 when symptoms are present (AIII).• If SARS-CoV-2 is detected or if infection is strongly suspected, donation should be deferred (BIII). <p>Transplant and Cellular Therapy Recipients with COVID-19</p> <ul style="list-style-type: none">• Clinicians should follow the guidelines for evaluating and managing COVID-19 in nontransplant patients when treating transplant and cellular therapy recipients (AIII). See Clinical Presentation of People with SARS-CoV-2 Infection, Antiviral Drugs That Are Approved or Under Evaluation for the Treatment of COVID-19, and Immunomodulators Under Evaluation for Treatment of COVID-19 for more information.• The Panel recommends that clinicians who are treating COVID-19 in transplant and cellular therapy patients consult with a transplant specialist before adjusting immunosuppressive medications (AIII).• When treating COVID-19, clinicians should pay careful attention to potential drug-drug interactions and overlapping toxicities with immunosuppressants, prophylactic antimicrobials, and other medications (AIII).
<p>Rating of Recommendations: A = Strong; B = Moderate; C = Optional</p> <p>Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion</p>

Introduction

Treating COVID-19 in solid organ transplant (SOT), hematopoietic cell transplant (HCT), and cellular immunotherapy recipients can be challenging due to the presence of coexisting medical conditions, transplant-related cytopenias, and the need for chronic immunosuppressive therapy to prevent graft rejection and graft-versus-host disease. Transplant recipients may also potentially have increased exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) given their frequent contact with the health care system. Since immunosuppressive agents modulate several aspects of the host's immune response, the severity of COVID-19 could potentially be affected by the type and the intensity

of the immunosuppressive effect of the agent, as well as by specific combinations of immunosuppressive agents. Some transplant recipients have medical comorbidities that have been associated with more severe cases of COVID-19 and a greater risk of mortality, which makes the attributable impact of transplantation on disease severity difficult to assess.

The American Association for the Study of Liver Diseases (AASLD),¹ the [International Society for Heart and Lung Transplantation](#), the [American Society of Transplantation](#), the [American Society for Transplantation and Cellular Therapy](#) (ASTCT), the [European Society for Blood and Marrow Transplantation](#) (EBMT), and the [Association of Organ Procurement Organizations](#) provide guidance for clinicians who are caring for transplant recipients with COVID-19, as well as guidance for screening potential donors and transplant or cell therapy candidates. This section of the Guidelines complements these sources and focuses on considerations for managing COVID-19 in SOT, HCT, and cellular therapy recipients. The optimal management and therapeutic approach to COVID-19 in these populations is unknown. At this time, the procedures for evaluating and managing COVID-19 in transplant recipients are the same as for nontransplant patients (**AIII**). See [Clinical Presentation of People with SARS-CoV-2 Infection](#), [Antiviral Drugs That Are Approved or Under Evaluation for the Treatment of COVID-19](#), and [Immunomodulators Under Evaluation for Treatment of COVID-19](#) for more information. The medications that are used to treat COVID-19 may present different risks and benefits to transplant patients and nontransplant patients.

Assessment of SARS-CoV-2 Infection in Transplant and Cellular Therapy Candidates and Donors

The risk of transmission of SARS-CoV-2 from donors to candidates is unknown. The probability of donor or candidate infection with SARS-CoV-2 may be estimated by considering epidemiologic risk, obtaining clinical history, and testing with molecular techniques. No current testing strategy is sensitive enough or specific enough to totally exclude active infection. Living solid organ donors should be counseled on strategies to prevent infection and monitored for exposures and symptoms in the 14 days prior to scheduled transplant.² HCT donors should practice good hygiene and avoid crowded places and large group gatherings during the 28 days prior to donation.³

Assessment of Transplant and Cellular Therapy Candidates

Diagnostic molecular testing for SARS-CoV-2 is recommended for all potential SOT candidates with signs and symptoms that suggest acute COVID-19 infection (**AIII**). All potential SOT candidates should be assessed for exposure to COVID-19 and clinical symptoms that are compatible with COVID-19 before they are called in for transplantation and should undergo diagnostic molecular testing for SARS-CoV-2 shortly before SOT in accordance with guidance from medical professional organizations (**AIII**).

Clinicians should consider performing diagnostic testing for SARS-CoV-2 in all HCT and cellular therapy candidates who exhibit symptoms. All candidates should also undergo diagnostic molecular testing for SARS-CoV-2 shortly before HCT or cell therapy (**AIII**).

Assessment of Donors

The COVID-19 Treatment Guidelines Panel (the Panel) recommends following the guidance from medical professional organizations and assessing all potential HCT donors for exposure to COVID-19 and clinical symptoms that are compatible with COVID-19 before donation (**AIII**). Deceased donors should undergo screening for known symptoms and exposure to others with COVID-19 before transplantation, and decisions about using such organs should be made on a case-by-case basis (**BIII**). Recommendations for screening are outlined in the ASTCT and EBMT guidelines.

If SARS-CoV-2 Infection Is Detected or Strongly Suspected

If SARS-CoV-2 is detected or if infection is strongly suspected in a potential SOT donor or candidate, transplant should be deferred, if possible (**BIII**). The optimal disease-free interval before transplantation is not known. The risks of viral transmission should be balanced against the risks to the candidate, such as progression of the underlying disease and risk of mortality if the candidate does not receive the transplant. This decision should be continually reassessed as conditions evolve. For HCT and cellular therapy candidates, current guidelines recommend deferring transplants or immunotherapy procedures, including peripheral blood stem cell mobilization, bone marrow harvest, T cell collection, and conditioning/lymphodepletion in recipients who test positive for SARS-CoV-2 or who have clinical symptoms that are consistent with infection. Final decisions should be made on a case-by-case basis while weighing the risks of delaying or altering therapy for the underlying disease.

Transplant Recipients with COVID-19

SOT recipients who are receiving immunosuppressive therapy should be considered to be at increased risk for severe COVID-19.^{1,4} A national survey of 88 U.S. transplant centers conducted between March 24 and 31, 2020, reported that 148 SOT recipients received a diagnosis of COVID-19 infection (69.6% were kidney recipients, 15.5% were liver recipients, 8.8% were heart recipients, and 6.1% were lung recipients).⁵ COVID-19 was mild in 54% of recipients and moderate in 21% of recipients, and 25% of recipients were critically ill. Modification of immunosuppressive therapy during COVID-19 and the use of investigational therapies for treatment of COVID-19 varied widely among recipients. Initial reports of transplant recipients who were hospitalized with COVID-19 suggest mortality rates of up to 28%.⁶⁻⁹

Risk of Graft Rejection

There have been no published reports of graft rejection in SOT recipients who received a diagnosis of COVID-19, although this may be due to a limited ability to perform biopsies. Acute cellular rejection should not be presumed in SOT recipients without biopsy confirmation in individuals with or without COVID-19. Similarly, immunosuppressive therapy should be initiated in recipients with or without COVID-19 who have rejection confirmed by a biopsy.¹

There is a lack of data on the incidence and clinical characteristics of SARS-CoV-2 infection in [HCT](#) and [cellular therapy recipients](#). Experience with other respiratory viruses suggests that this population is at a high risk for severe disease, including increased rates of lower respiratory tract infection and mortality.¹⁰ Factors that may determine clinical severity include degree of cytopenia, time since transplant, intensity of the conditioning regimen, graft source, degree of mismatch, and the need for further immunosuppression to manage graft-versus-host disease. For other respiratory viruses, HCT recipients often exhibit prolonged viral shedding,¹¹⁻¹⁴ which can have implications for infection prevention and for the timing of potential interventions.

Treatment of COVID-19 in Transplant Recipients

Currently, remdesivir, an antiviral agent, is the only drug approved by the Food and Drug Administration (FDA) for the treatment of COVID-19.

Preliminary data from a large randomized controlled trial have shown that a short course of dexamethasone (6 mg once daily for up to 10 days) can improve survival in patients with COVID-19 who are mechanically ventilated or who require supplemental oxygen.¹⁵ At this time, the risks and benefits of using dexamethasone in transplant recipients with COVID-19 who are receiving immunosuppressive therapy, which may include corticosteroids, are unknown.

The Panel's recommendations for the use of remdesivir and dexamethasone in patients with COVID-19

can be found in the [Therapeutic Management](#) section.

A number of other investigational agents and drugs that are approved by the FDA for other indications are being evaluated for the treatment of COVID-19 (e.g., [antiviral therapies](#), [COVID-19 convalescent plasma](#)) and its associated complications (e.g., [immunomodulators](#), [antithrombotic agents](#)). In general, the considerations when treating COVID-19 are the same for transplant recipients as for the general population. When possible, treatment should be given as part of a clinical trial. The safety and efficacy of investigational agents and drugs that have been approved by the FDA for other indications are not well defined in transplant recipients. Moreover, it is unknown whether concomitant use of immunosuppressive agents to prevent allograft rejection in the setting of COVID-19 affects treatment outcome.

The use of antiviral or immune-based therapies for the treatment of COVID-19 can present additional challenges in transplant patients. Clinicians should pay special attention to the potential for drug-drug interactions and overlapping toxicities with concomitant medications, such as immunosuppressants that are used to prevent allograft rejection (e.g., corticosteroids, mycophenolate, and calcineurin inhibitors such as tacrolimus and cyclosporine), antimicrobials that are used to prevent opportunistic infections, and other medications. Dose modifications may be necessary for drugs that are used to treat COVID-19 in transplant recipients with pre-existing organ dysfunction. Adjustments to the immunosuppressive regimen should be individualized based on disease severity, the specific immunosuppressants used, the type of transplant, the time since transplantation, the drug concentration, and the risk of graft rejection.⁷ Clinicians who are treating COVID-19 in transplant patients should consult with a transplant specialist before adjusting immunosuppressive medication (**AIII**).

Certain therapeutics (e.g., remdesivir, tocilizumab) are associated with elevated levels of transaminases. For liver transplant recipients, the AASLD does not view abnormal liver biochemistries as a contraindication to using investigational or off-label therapeutics, although certain elevation thresholds may exclude patients from trials of some investigational agents.¹⁶ Close monitoring of liver biochemistries is warranted in patients with COVID-19, especially when they are receiving agents with a known risk of hepatotoxicity.

Calcineurin inhibitors, which are commonly used to prevent allograft rejection, have a narrow therapeutic index. Medications that inhibit or induce cytochrome P450 enzymes or P-glycoprotein may put patients who receive calcineurin inhibitors at risk of clinically significant drug-drug interactions, increasing the need for therapeutic drug monitoring and the need to assess for signs of toxicity or rejection.¹⁷ Similarly, transplant patients may be at a higher risk of adverse effects, particularly when their concomitant medications have overlapping toxicities. Specific concerns about the use of potential antiviral medications and immune-based therapy for COVID-19 in transplant patients are noted below. See Tables [2d](#) and [4b](#) for additional details.

Table 5. Special Concerns for Drugs That Are Being Evaluated for COVID-19 Treatment in Transplant Patients

Last Updated: November 3, 2020

Drugs That Are Being Evaluated for COVID-19 Treatment	Concerns in Transplant Patients
Azithromycin	<ul style="list-style-type: none"> • Hepatotoxicity (cholestatic hepatitis, rare) • Additive effect with other drugs that prolong the QTc interval.
Chloroquine and Hydroxychloroquine	<ul style="list-style-type: none"> • Moderate inhibition of CYP2D6. • Inhibition of P-gp may increase levels of calcineurin inhibitors and mTOR inhibitors. • Additive effect with other drugs that prolong the QTc interval.
Dexamethasone	<ul style="list-style-type: none"> • Moderate CYP3A4 inducer • Potential for additional immunosuppression and increased risk of OIs.
HIV Protease Inhibitors	<ul style="list-style-type: none"> • RTV and other PIs are strong inhibitors of CYP3A4. Coadministration will increase concentrations of tacrolimus, cyclosporine, everolimus, sirolimus, and prednisone. • TDM and dose adjustment of immunosuppressant is necessary. Monitor for calcineurin inhibitor-associated toxicities.
Interleukin-6 Inhibitors	<ul style="list-style-type: none"> • Use of IL-6 inhibitors may lead to increased metabolism of drugs that are CYP substrates. Effects on CYP may persist for weeks after therapy. • AEs include neutropenia and an increase in transaminases. See Table 4b.
Remdesivir	<ul style="list-style-type: none"> • Increase in levels of serum transaminases. • Accumulation of drug vehicle cyclodextrin in patients with kidney dysfunction.
Ribavirin	<ul style="list-style-type: none"> • Significant toxicities, including anemia, bradycardia, and an increase in serum transaminases levels.

Key: AE = adverse effects; CYP = cytochrome P450; IL = interleukin; mTOR = mechanistic target of rapamycin; OI = opportunistic infection; P-gp = P-glycoprotein; PI = protease inhibitor; RTV= ritonavir; TDM = therapeutic drug monitoring

References

1. Fix OK, Hameed B, Fontana RJ, et al. Clinical best practice advice for hepatology and liver transplant providers during the COVID-19 pandemic: AASLD Expert Panel consensus statement. *Hepatology*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32298473>.
2. American Society of Transplantation. COVID-19 resources for transplant community. 2020. Available at: <https://www.covid19treatmentguidelines.nih.gov/contact-us/>. Accessed June 26, 2020.
3. American Society for Transplantation and Cellular Therapy. ASTCT interim patient guidelines April 20, 2020. 2020. Available at: <https://www.astct.org/viewdocument/astct-interim-patient-guidelines-ap?CommunityKey=d3949d84-3440-45f4-8142-90ea05adb0e5&tab=librarydocuments>. Accessed July 2, 2020.
4. Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19): groups at higher risk for severe illness. 2020. Available at: <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/groups-at-higher-risk.html>. Accessed June 1, 2020.
5. Boyarsky BJ, Po-Yu Chiang T, Werbel WA, et al. Early impact of COVID-19 on transplant center practices and policies in the United States. *Am J Transplant*. 2020;20(7):1809-1818. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32282982>.

6. Akalin E, Azzi Y, Bartash R, et al. COVID-19 and kidney transplantation. *N Engl J Med*. 2020;382(25):2475-2477. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32329975>.
7. Pereira MR, Mohan S, Cohen DJ, et al. COVID-19 in solid organ transplant recipients: Initial report from the US epicenter. *Am J Transplant*. 2020;20(7):1800-1808. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32330343>.
8. Alberici F, Delbarba E, Manenti C, et al. A single center observational study of the clinical characteristics and short-term outcome of 20 kidney transplant patients admitted for SARS-CoV2 pneumonia. *Kidney Int*. 2020;97(6):1083-1088. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32354634>.
9. Montagud-Marrahi E, Cofan F, Torregrosa JV, et al. Preliminary data on outcomes of SARS-CoV-2 infection in a Spanish single center cohort of kidney recipients. *Am J Transplant*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32368838>.
10. Ison MG, Hirsch HH. Community-acquired respiratory viruses in transplant patients: diversity, impact, unmet clinical needs. *Clin Microbiol Rev*. 2019;32(4). Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31511250>.
11. Ogimi C, Xie H, Leisenring WM, et al. Initial high viral load is associated with prolonged shedding of human rhinovirus in allogeneic hematopoietic cell transplant recipients. *Biol Blood Marrow Transplant*. 2018;24(10):2160-2163. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30009982>.
12. Ogimi C, Greninger AL, Waghmare AA, et al. Prolonged shedding of human coronavirus in hematopoietic cell transplant recipients: risk factors and viral genome evolution. *J Infect Dis*. 2017;216(2):203-209. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28838146>.
13. Milano F, Campbell AP, Guthrie KA, et al. Human rhinovirus and coronavirus detection among allogeneic hematopoietic stem cell transplantation recipients. *Blood*. 2010;115(10):2088-2094. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20042728>.
14. Choi SM, Boudreault AA, Xie H, Englund JA, Corey L, Boeckh M. Differences in clinical outcomes after 2009 influenza A/H1N1 and seasonal influenza among hematopoietic cell transplant recipients. *Blood*. 2011;117(19):5050-5056. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21372154>.
15. Horby P, Shen Lim W, Emberson J, et al. Effect of dexamethasone in hospitalized patients with COVID-19: preliminary report. *medRxiv*. 2020;Preprint. Available at: <https://www.medrxiv.org/content/10.1101/2020.06.22.20137273v1>.
16. American Association for the Study of Liver Diseases. Clinical insights for hepatology and liver transplant providers during the COVID-19 pandemic. 2020. Available at: <https://www.aasld.org/sites/default/files/2020-04/AASLD-COVID19-ClinicalInsights-4.07.2020-Final.pdf>. Accessed: June 26, 2020.
17. Elens L, Langman LJ, Hesselink DA, et al. Pharmacologic treatment of transplant recipients infected with SARS-CoV-2: considerations regarding therapeutic drug monitoring and drug-drug interactions. *Ther Drug Monit*. 2020;42(3):360-368. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32304488>.

Special Considerations in People With Human Immunodeficiency Virus

Last Updated: October 9, 2020

Summary Recommendations
<p>Prevention and Diagnosis of COVID-19</p> <ul style="list-style-type: none">The COVID-19 Treatment Guidelines Panel recommends using the same approach for the prevention and diagnosis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in people with human immunodeficiency virus (HIV) as in people without HIV (AIII).
<p>Management of COVID-19</p> <ul style="list-style-type: none">Recommendations for the triage, management, and treatment of COVID-19 in people with HIV are the same as those for the general population (AIII).In people with advanced HIV and suspected or documented COVID-19, HIV-associated opportunistic infections (OIs) should also be considered in the differential diagnosis of febrile illness (AIII).When starting treatment for COVID-19 in a patient with HIV, clinicians should pay careful attention to potential drug-drug interactions and overlapping toxicities among COVID-19 treatments, antiretroviral (ARV) medications, antimicrobial therapies, and other medications (AIII).People with HIV should be offered the opportunity to participate in clinical trials of vaccines and potential treatments for SARS-CoV-2 infection.
<p>Management of HIV</p> <ul style="list-style-type: none">People with HIV who develop COVID-19, including those who require hospitalization, should continue their antiretroviral therapy (ART) and OI prophylaxis whenever possible (AIII).Clinicians treating COVID-19 in people with HIV should consult with an HIV specialist before adjusting or switching ARV medications (AIII).An ART regimen should not be switched or adjusted (i.e., by adding ARVs to the regimen) for the purpose of preventing or treating SARS-CoV-2 infection (AIII).For people who present with COVID-19 and a new diagnosis of HIV, clinicians should consult an HIV specialist to determine the optimal time to initiate ART (see text for more detailed discussion).
<p>Rating of Recommendations: A = Strong; B = Moderate; C = Optional</p> <p>Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion</p>

Introduction

Approximately 1.2 million persons in the United States are living with human immunodeficiency virus (HIV). Most of these individuals are in care, and many are on antiretroviral therapy (ART) and have well-controlled disease.¹ Similar to COVID-19, HIV disproportionately affects racial and ethnic minorities and persons of lower socioeconomic status in the United States;² these demographic groups also appear to have a higher risk for worse outcomes with COVID-19. Information on HIV and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) coinfection is evolving rapidly. The sections below outline the current state of knowledge regarding the prevention and diagnosis of SARS-CoV-2 infection in people with HIV, treatment and clinical outcomes in people with HIV who develop COVID-19, and management of HIV during the COVID-19 pandemic. In addition to these Guidelines, the Department of Health and Human Services (HHS) Panel on Antiretroviral Guidelines for Adults and Adolescents has developed the [Interim Guidance for COVID-19 and Persons with HIV](#).

Prevention of COVID-19 in People With HIV

The COVID-19 Treatment Guidelines Panel (the Panel) recommends using the same approach in advising persons with HIV on the strategies to prevent acquisition of SARS-CoV-2 infection as used for people without HIV (**AIII**). There is currently no clear evidence that any antiretroviral (ARV) medications can prevent the acquisition of SARS-CoV-2 infection.

Diagnostic and Laboratory Testing for COVID-19 in People With HIV

Diagnosis of COVID-19 in People With HIV

The Panel recommends using the same approach for diagnosis of SARS-CoV-2 infection in people with HIV as in those without HIV (see [SARS-CoV-2 Testing](#)) (**AIII**). There is currently no evidence that the performance characteristics of nucleic acid amplification testing (NAAT) for diagnosis of acute SARS-CoV-2 infection differ in people with and without HIV. The Panel **recommends against** the use of serologic testing as the sole basis for diagnosis of acute SARS-CoV-2 infection. However, if diagnostic serologic testing is performed, the results should be interpreted with caution, especially in patients with HIV because cross-reactivity between antibodies to SARS-CoV-2 and HIV has been reported.³

Correlation of CD4 Count in People With HIV and COVID-19

The normal range of CD4 T lymphocyte (CD4) cell counts in healthy adults is about 500 to 1,600 cells/mm³. Persons with HIV and CD4 count of ≥ 500 cells/mm³ have similar cellular immune function to persons without HIV. In people with HIV, a CD4 count < 200 cells/mm³ meets the definition for AIDS. For patients on ART, the hallmark of treatment success is plasma HIV RNA below the level of detection by a PCR assay. Lymphopenia is a common laboratory finding in patients with COVID-19; in patients with HIV, clinicians should note that CD4 counts obtained during acute COVID-19 may not accurately reflect the patient's HIV disease stage.

There have been some reports of persons with advanced HIV who have presented with COVID-19 and another coinfection, including *Pneumocystis jirovecii* pneumonia.^{4,5} In patients with advanced HIV with suspected or confirmed SARS-CoV-2 infection, clinicians should consider a broader differential diagnosis for clinical symptoms and consider consultation with an HIV specialist (**AIII**).

Clinical Presentation of COVID-19 in People With HIV

It is currently not known whether the incidence of SARS-CoV-2 infection or the rate of progression to symptomatic disease is higher in persons with HIV. Approximately 50% of persons with HIV in the United States are aged > 50 years and many have comorbidities that are associated with more severe illness with COVID-19, including hypertension, diabetes mellitus, cardiovascular disease, tobacco use disorder, chronic lung disease, chronic liver disease, and cancer.⁶

There are several case reports and case series that describe the clinical presentation of COVID-19 in persons with HIV.⁷⁻¹⁷ These studies indicate that the clinical presentation of COVID-19 is similar in persons with and without HIV. Most of the published reports describe populations in which most of the individuals with HIV are on ART and have virologic suppression. Consequently, the current understanding of the impact of COVID-19 in persons with advanced HIV with low CD4 counts or those with persistent HIV viremia is limited.

Management of COVID-19 in People With HIV

Recommendations for the triage and management of COVID-19 in people with HIV are the same as those for the general population (**AIII**).

The treatment of COVID-19 in persons with HIV is the same as that for persons without HIV **(AIII)**. When starting treatment for COVID-19 in patients with HIV, clinicians should pay careful attention to potential drug-drug interactions and overlapping toxicities among COVID-19 treatments, ARV medications, antimicrobial therapies, and other medications **(AIII)**. [Remdesivir](#) should be used as recommended in the [Remdesivir](#) section of these Guidelines. There are no significant drug-drug interactions expected between remdesivir and ARV drugs. Dexamethasone should also be used as recommended in the [Corticosteroids](#) section of these Guidelines. Dexamethasone is an inducer of hepatic enzymes and could potentially lower levels of certain coadministered ARV drugs. However, this interaction is not expected to be clinically significant based on the short duration of dexamethasone therapy (up to 10 days) in the RECOVERY trial. Although some ARV drugs are being studied for the prevention and treatment of COVID-19, no agents have been shown to be effective.

People with HIV should be offered the opportunity to participate in clinical trials of vaccines and potential treatments for COVID-19. A variety of immunomodulatory therapies are prescribed empirically or administered as part of a clinical trial to treat severe COVID-19 disease. Data about whether these medications are safe to use in patients with HIV are lacking. If a medication is proven to reduce the mortality of patients with COVID-19 in the general population, it should also be used to treat COVID-19 in patients with HIV, unless data indicate that the medication is not safe or effective in this population.

Management of HIV in People With SARS-CoV-2/HIV Coinfection

Below are some general considerations regarding the management of HIV in people with SARS-CoV-2/HIV coinfection.

- ART and opportunistic infection prophylaxis should be continued in a patient with HIV who develops COVID-19, including in those who require hospitalization, whenever possible **(AIII)**. ARV treatment interruption may lead to rebound viremia, and in some cases, emergence of drug resistance. If the ARV drugs are not on the hospital's formulary, administer medications from the patient's home supplies (if available).
- Clinicians treating COVID-19 in people with HIV should consult with an HIV specialist before adjusting or switching a patient's ARV medications. An ART regimen should not be switched or adjusted (i.e., by adding ARVs to the regimen) for the purpose of preventing or treating SARS-CoV-2 infection **(AIII)**. Many drugs, including some ARV agents (e.g., lopinavir/ritonavir, boosted darunavir, and tenofovir disoproxil fumarate/emtricitabine), have been or are being evaluated in clinical trials or are prescribed for off-label use for the treatment or prevention of SARS-CoV-2 infection. To date, lopinavir/ritonavir and darunavir/ritonavir have not been found to be effective (see [Antiviral Therapy](#)).^{18,19} Two retrospective studies suggest an effect of tenofovir disoproxil fumarate/emtricitabine in preventing SARS-CoV-2 acquisition or hospitalization or death associated with COVID-19;^{8,20} however, the significance of these findings is unclear as neither study adequately controlled for confounding variables such as age and comorbidities.
- For patients who are taking an investigational ARV medication as part of their HIV regimen, arrangements should be made with the investigational study team to continue the medication, if possible.
- For critically ill patients who require tube feeding, some ARV medications are available in liquid formulations and some, but not all, ARV pills may be crushed. Clinicians should consult an HIV specialist and/or pharmacist to assess the best way for a patient with a feeding tube to continue an effective ARV regimen. Information may be available in the drug product label or in [this document](#).
- For people who present with COVID-19 and have either a new diagnosis of HIV or a history of

HIV but are not taking ART, the optimal time to start or restart ART is currently unknown. For people with HIV who have not initiated ART or who have been off therapy for >2 weeks before presenting with COVID-19, the Panel recommends consultation with an HIV specialist regarding initiation or re-initiation of ART as soon as clinically feasible. If ART is started, maintaining treatment and linking patients to HIV care upon hospital discharge is critical. If an HIV specialist is not available, clinical consultation is available through the [National Clinical Consultation Center warmline](#), Monday through Friday, 9 am to 8 pm EST.

Clinical Outcomes of COVID-19 in People With HIV

No significant differences in clinical outcomes have been noted in several small case series from Europe and the United States.^{7,9-11,13-17} Data from the Veterans Aging Cohort Study were analyzed to compare outcomes in 253 mostly male participants with HIV and COVID-19 who were matched with 504 participants with only COVID-19.¹² In this comparison, there was no difference in COVID-19-related hospitalization, intensive care unit admission, intubation, or death in patients with or without HIV. In contrast, worse outcomes, including increased COVID-19 mortality rates, in people with HIV have been reported in cohort studies from the United States, the United Kingdom, and South Africa.²⁰⁻²³ In a multicenter cohort study of 286 patients with HIV and COVID-19 in the United States, lower CD4 count (i.e., <200 cells/mm³), despite virologic suppression, was associated with a higher risk for poor outcomes.²³

Special Considerations in Children and Pregnant Women With HIV Who Develop COVID-19

Currently, there is limited information about pregnancy and maternal outcomes in women with HIV who have COVID-19 and in children with HIV and COVID-19. Readers are referred to sections in these Guidelines on the management of COVID-19 in [pregnancy](#) and in [children](#), and to the [HHS Interim Guidance for COVID-19 and Persons with HIV](#).

References

1. Harris NS, Johnson AS, Huang YA, et al. Vital signs: status of human immunodeficiency virus testing, viral suppression, and HIV preexposure prophylaxis—United States, 2013–2018. *MMWR Morb Mortal Wkly Rep*. 2019;68(48):1117-1123. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31805031>.
2. Meyerowitz EA, Kim AY, Ard KL, et al. Disproportionate burden of coronavirus disease 2019 among racial minorities and those in congregate settings among a large cohort of people with HIV. *AIDS*. 2020;34(12):1781-1787. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32604138>.
3. Food and Drug Administration. New York SARS-CoV-2 real-time reverse transcriptase (RT)-PCR diagnostic panel. 2020. Available at: <https://www.fda.gov/media/135847/download>. Accessed September 8, 2020.
4. Coleman H, Snell LB, Simons R, Douthwaite ST, Lee MJ. Coronavirus disease 2019 and *Pneumocystis jirovecii* pneumonia: a diagnostic dilemma in HIV. *AIDS*. 2020;34(8):1258-1260. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32501852>.
5. Blanco JL, Ambrosioni J, Garcia F, et al. COVID-19 in patients with HIV: clinical case series. *Lancet HIV*. 2020;7(5):e314-e316. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32304642>.
6. Centers for Disease Control and Prevention. HIV surveillance report: estimated HIV incidence and prevalence in the United States 2014-2018. 2020. Available at: <https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-supplemental-report-vol-25-1.pdf>. Accessed: September 8, 2020.
7. Byrd KM, Beckwith CG, Garland JM, et al. SARS-CoV-2 and HIV coinfection: clinical experience from Rhode Island, United States. *J Int AIDS Soc*. 2020;23(7):e25573. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32657527>.

8. Del Amo J, Polo R, Moreno S, et al. Incidence and Severity of COVID-19 in HIV-Positive Persons Receiving Antiretroviral Therapy: a cohort study. *Ann Intern Med*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32589451>.
9. Gervasoni C, Meraviglia P, Riva A, et al. Clinical features and outcomes of HIV patients with coronavirus disease 2019. *Clin Infect Dis*. 2020; Published online ahead of print. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32407467>.
10. Harter G, Spinner CD, Roider J, et al. COVID-19 in people living with human immunodeficiency virus: a case series of 33 patients. *Infection*. 2020; Published online ahead of print. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32394344>.
11. Karmen-Tuohy S, Carlucci PM, Zervou FN, et al. Outcomes Among HIV-Positive Patients Hospitalized With COVID-19. *J Acquir Immune Defic Syndr*. 2020;85(1):6-10. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32568770>.
12. Park LS, Rentsch CT, Sigel K, et al. COVID-19 in the largest U.S. cohort. Presented at: 23rd International AIDS Conference. 2020. Virtual.
13. Patel VV, Felsen UR, Fisher M, et al. Clinical outcomes by HIV serostatus, CD4 count, and viral suppression among people hospitalized with COVID-19 in the Bronx, New York. Presented at: 23rd International AIDS Conference. 2020. Virtual.
14. Shalev N, Scherer M, LaSota ED, et al. Clinical characteristics and outcomes in people living with HIV hospitalized for COVID-19. *Clin Infect Dis*. 2020; Published online ahead of print. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32472138>.
15. Sigel K, Swartz T, Golden E, et al. COVID-19 and people with HIV infection: outcomes for hospitalized patients in New York City. *Clin Infect Dis*. 2020; Published online ahead of print. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32594164>.
16. Stoeckle K, Johnston CD, Jannat-Khah DP, et al. COVID-19 in hospitalized adults with HIV. *Open Forum Infect Dis*. 2020;7(8). Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32864388>.
17. Vizcarra P, Perez-Elias MJ, Quereda C, et al. Description of COVID-19 in HIV-infected individuals: a single-centre, prospective cohort. *Lancet HIV*. 2020;7(8):e554-e564. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32473657>.
18. 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: <https://www.ncbi.nlm.nih.gov/pubmed/32187464>.
19. Chen J, Xia L, Liu L, et al. Antiviral activity and safety of darunavir/cobicistat for the treatment of COVID-19. *Open Forum Infect Dis*. 2020;7(7):ofaa241. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32671131>.
20. Davies MA. HIV and risk of COVID-19 death: a population cohort study from the Western Cape Province, South Africa. *medRxiv*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32637972>.
21. Bhaskaran K, Rentsch CT, MacKenna B, et al. HIV infection and COVID-19 death: population-based cohort analysis of UK primary care data and linked national death registrations within the OpenSAFELY platform. *medRxiv*. 2020. Available at: <https://www.medrxiv.org/content/10.1101/2020.08.07.20169490v1>.
22. Geretti A, Stockdale A, Kelly S, et al. Outcomes of COVID-19 related hospitalisation among people with HIV in the ISARIC WHO Clinical Characterisation Protocol UK Protocol: prospective observational study. *medRxiv*. 2020. Available at: <https://www.medrxiv.org/content/10.1101/2020.08.07.20170449v1>.
23. Dandachi D, Geiger G, Montgomery MW, et al. Characteristics, comorbidities, and outcomes in a multicenter registry of patients with HIV and coronavirus disease-19. *Clin Infect Dis*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32905581>.

Influenza and COVID-19

Last Updated: October 22, 2020

Summary Recommendations

Influenza Vaccination

- Although data are lacking on influenza vaccination for persons with COVID-19, on the basis of practice for other acute respiratory infections, the Panel recommends that persons with COVID-19 should receive an inactivated influenza vaccine (**BIII**). The Centers for Disease Control and Prevention (CDC) has provided guidance on the timing of influenza vaccination for inpatients and outpatients with COVID-19 (see [Interim Guidance for Routine and Influenza Immunization Services During the COVID-19 Pandemic](#)).

Diagnosis of Influenza and COVID-19 When Influenza Viruses and SARS-CoV-2 Are Cocirculating

- Only testing can distinguish between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and influenza virus infections and identify SARS-CoV-2 and influenza virus coinfection.
- When SARS-CoV-2 and influenza viruses are cocirculating, the Panel recommends testing for both viruses in all hospitalized patients with acute respiratory illness (**AIII**).
- When SARS-CoV-2 and influenza viruses are cocirculating, the Panel recommends influenza testing in outpatients with acute respiratory illness if the results will change clinical management of the patient (**BIII**).
- Testing for other pathogens should be considered depending on clinical circumstances, especially in patients with influenza in whom bacterial superinfection is a well-recognized complication.
- See the CDC [Information for Clinicians on Influenza Virus Testing](#) and the [Infectious Diseases Society of America \(IDSA\) Clinical Practice Guidelines](#) for more information.

Antiviral Treatment of Influenza When Influenza Viruses and SARS-CoV-2 Are Cocirculating

- The treatment of influenza is the same in all patients regardless of SARS-CoV-2 coinfection (**AIII**).
- The Panel recommends that hospitalized patients be started on empiric treatment for influenza with oseltamivir as soon as possible without waiting for influenza testing results (**AIIb**).
 - Antiviral treatment of influenza can be stopped when influenza has been ruled out by nucleic acid detection assay in upper respiratory tract specimens for nonintubated patients and in both upper and lower respiratory tract specimens for intubated patients.
- For influenza treatment in hospitalized and non-hospitalized patients, see the [CDC](#) and [IDSA](#) recommendations on antiviral treatment of influenza.

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

Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

Introduction

Influenza activity in the United States during the 2020–2021 influenza season is difficult to predict and could vary geographically and by the extent of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) community mitigation measures. During early 2020, sharp declines in influenza activity coincided with implementation of SARS-CoV-2 control measures in the United States and several Asian countries.¹⁻⁴ Very low influenza virus circulation was observed in Australia, Chile, and South Africa during the typical Southern Hemisphere influenza season in 2020.⁵ Clinicians should monitor local influenza and SARS-CoV-2 activity (e.g., by tracking local and state public health surveillance data and testing performed at health care facilities) to inform evaluation and management of patients with acute respiratory illness.

Influenza Vaccination

There are no data on the safety, immunogenicity, or effectiveness of influenza vaccines in patients with mild COVID-19 or those who are recovering from COVID-19. Therefore, the optimal timing for influenza vaccination in these patients is unknown. The safety and efficacy of vaccinating persons who have mild illnesses from other etiologies have been documented.⁶ On the basis of practice following other acute respiratory infections, the Panel recommends that persons with COVID-19 should receive an inactivated influenza vaccine (**BIII**). The Centers for Disease Control and Prevention (CDC) has provided guidance on the timing of influenza vaccination for inpatients and outpatients with COVID-19 (see [Interim Guidance for Routine and Influenza Immunization Services During the COVID-19 Pandemic](#)). It is not known whether dexamethasone or other immunomodulatory therapies for COVID-19 will affect the immune response to influenza vaccine. However, despite this uncertainty, as long as influenza viruses are circulating, an unvaccinated person with COVID-19 should receive the influenza vaccine once they have substantially improved or recovered from COVID-19. See influenza vaccine recommendations from [CDC](#) and the [Advisory Committee on Immunization Practices](#).

Clinical Presentation of Influenza Versus COVID-19

The signs and symptoms of uncomplicated, clinically mild influenza overlap with those of mild COVID-19. Ageusia and anosmia can occur with both diseases, but these symptoms are more common with COVID-19 than with influenza. Fever is not always present in patients with either disease, particularly in patients who are immunosuppressed or elderly. Complications of influenza and COVID-19 can be similar, but the onset of influenza complications and severe disease typically occurs within a week of illness onset whereas the onset of severe COVID-19 usually occurs in the second week of illness. Because of the overlap in signs and symptoms, when SARS-CoV-2 and influenza viruses are cocirculating, diagnostic testing for both viruses in people with an acute respiratory illness is needed to distinguish between SARS-CoV-2 and influenza virus, and to identify SARS-CoV-2 and influenza virus coinfection. Coinfection with influenza A or B viruses and SARS-CoV-2 has been described in case reports and case series,⁷⁻¹¹ but the frequency, severity, and risk factors for coinfection with these viruses versus for infection with either virus alone are unknown.

Which Patients Should be Tested for SARS-CoV-2 and influenza?

When influenza viruses and SARS-CoV-2 are cocirculating in the community, SARS-CoV-2 testing and influenza testing should be performed in all patients hospitalized with suspected COVID-19 or influenza (see [Testing for SARS-CoV-2 Infection](#)) (**AIII**). When influenza viruses and SARS-CoV-2 are cocirculating in the community, SARS-CoV-2 testing should be performed in outpatients with suspected COVID-19, and influenza testing can be considered in outpatients with suspected influenza if the results will change clinical management of the illness (**BIII**). Several multiplex assays that detect SARS-CoV-2 and influenza A and B viruses have received Food and Drug Administration Emergency Use Authorization and can provide results in 15 minutes to 8 hours on a single respiratory specimen.^{12,13} For information on available influenza tests, including clinical algorithms for testing of patients when SARS-CoV-2 and influenza viruses are cocirculating, see the [CDC Information for Clinicians on Influenza Virus Testing](#) and [recommendations of the Infectious Diseases Society of America \(IDSA\)](#) on the use of influenza tests and interpretation of testing results.¹⁴

Which Patients Should Receive Antiviral Treatment of Influenza?

When SARS-CoV-2 and influenza viruses are cocirculating in the community, patients who require hospitalization and are suspected of having either or both viral infections should receive influenza antiviral treatment with oseltamivir as soon as possible without waiting for influenza testing results

(AIIb).¹⁴ Treatment for influenza is the same for all patients regardless of SARS-CoV-2 coinfection (AIII). See the [CDC Influenza Antiviral Medications: Summary for Clinicians](#), including [clinical algorithms](#) for antiviral treatment of patients with suspected or confirmed influenza when SARS-CoV-2 and influenza viruses are cocirculating, and the [IDSA Clinical Practice Guidelines](#) recommendations on antiviral treatment of influenza.

If a diagnosis of COVID-19 or another etiology is confirmed and if the result of an influenza nucleic acid detection assay from an upper respiratory tract specimen is negative:

- *In a Patient Who is Not Intubated:* Antiviral treatment for influenza can be stopped.
- *In a Patient Who is Intubated:* Antiviral treatment for influenza should be continued and if a lower respiratory tract specimen (e.g., endotracheal aspirate) can be safely obtained, it should be tested by influenza nucleic acid detection. If the lower respiratory tract specimen is also negative, influenza antiviral treatment can be stopped.

Treatment Considerations for Hospitalized Patients With Suspected or Confirmed SARS-CoV-2 and Influenza Virus Coinfection

- Corticosteroids, which may be used for the treatment of COVID-19, may prolong influenza viral replication and viral RNA detection and may be associated with poor outcomes.^{14,15}
- Oseltamivir has no activity against SARS-CoV-2.¹⁶ Oseltamivir does not have any known interactions with remdesivir.
- Standard-dose oseltamivir is well absorbed even in critically ill patients. For patients who cannot tolerate oral or enterically administered oseltamivir (e.g., because of gastric stasis, malabsorption, or gastrointestinal bleeding), intravenous peramivir is an option.¹⁴ There are no data on peramivir activity against SARS-CoV-2.
- CDC does not recommend inhaled zanamivir and oral baloxavir for the treatment of influenza in hospitalized patients because of insufficient safety and efficacy data (see the [CDC Influenza Antiviral Medications: Summary for Clinicians](#)). There are no data on zanamivir activity against SARS-CoV-2. Baloxavir has no activity against SARS-CoV-2.¹⁶
- Based upon limited data, the co-occurrence of community-acquired secondary bacterial pneumonia with COVID-19 appears to be infrequent and may be more common with influenza.^{17,18} Typical bacterial causes of community-acquired pneumonia with severe influenza are *Staphylococcus aureus* (methicillin-resistant *S. aureus* [MRSA] and methicillin-susceptible *S. aureus* [MSSA]), *Streptococcus pneumoniae*, and group A *Streptococcus*.¹⁴
- Patients with COVID-19 who develop new respiratory symptoms with or without fever or respiratory distress, and without a clear diagnosis, should be evaluated for the possibility of nosocomial influenza.

References

1. Kuo SC, Shih SM, Chien LH, Hsiung CA. Collateral benefit of COVID-19 control measures on influenza activity, Taiwan. *Emerg Infect Dis*. 2020;26(8):1928-1930. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32339091>.
2. Soo RJJ, Chiew CJ, Ma S, Pung R, Lee V. Decreased influenza incidence under COVID-19 control measures, Singapore. *Emerg Infect Dis*. 2020;26(8):1933-1935. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32339092>.
3. Suntronwong N, Thongpan I, Chuchaona W, et al. Impact of COVID-19 public health interventions on influenza incidence in Thailand. *Pathog Glob Health*. 2020;114(5):225-227. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/32521210>.

4. Lei H, Xu M, Wang X, et al. Non-pharmaceutical interventions used to control COVID-19 reduced seasonal influenza transmission in China. *J Infect Dis*. 2020; Published online ahead of print. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32898256>.
5. Olsen SJ, Azziz-Baumgartner E, Budd AP, et al. Decreased influenza activity during the COVID-19 pandemic—United States, Australia, Chile, and South Africa, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(37):1305-1309. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32941415>.
6. Centers for Disease Control and Prevention. Contraindications and precautions. General best practice guidelines for immunization: best practices guidance of the advisory committee on immunization practices (ACIP). 2020. Available at: <https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html>. Accessed October 16, 2020.
7. Hashemi SA, Safamanesh S, Ghasemzadeh-Moghaddam H, Ghafouri M, Azimian A. High prevalence of SARS-CoV-2 and influenza A virus (H1N1) coinfection in dead patients in Northeastern Iran. *J Med Virol*. 2020; Published online ahead of print. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32720703>.
8. Huang BR, Lin YL, Wan CK, et al. Co-infection of influenza B virus and SARS-CoV-2: A case report from Taiwan. *J Microbiol Immunol Infect*. 2020; Published online ahead of print. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32646801>.
9. Yue H, Zhang M, Xing L, et al. The epidemiology and clinical characteristics of co-infection of SARS-CoV-2 and influenza viruses in patients during COVID-19 outbreak. *J Med Virol*. 2020; Published online ahead of print. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32530499>.
10. Cuadrado-Payan E, Montagud-Marrahi E, Torres-Elorza M, et al. SARS-CoV-2 and influenza virus co-infection. *Lancet*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32423586>.
11. Wu X, Cai Y, Huang X, et al. Co-infection with SARS-CoV-2 and influenza A virus in patient with pneumonia, China. *Emerg Infect Dis*. 2020;26(6):1324-1326. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32160148>.
12. Food and Drug Administration. Coronavirus disease 2019 (COVID-19) emergency use authorizations for medical devices. Individual EUAs for molecular diagnostic tests for SARS-CoV-2. 2020. Available at: <https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/vitro-diagnostics-euas#individual-molecular>. Accessed October 16, 2020.
13. Centers for Disease Control and Prevention. Table 4. Multiplex assays authorized for simultaneous detection of influenza viruses and SARS-CoV-2 by FDA. 2020. Available at: <https://www.cdc.gov/flu/professionals/diagnosis/table-flu-covid19-detection.html>. Accessed October 16, 2020.
14. Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical practice guidelines by the Infectious Diseases Society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza. *Clin Infect Dis*. 2019;68(6):e1-e47. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30566567>.
15. Zhou Y, Fu X, Liu X, et al. Use of corticosteroids in influenza-associated acute respiratory distress syndrome and severe pneumonia: a systemic review and meta-analysis. *Sci Rep*. 2020;10(1):3044. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32080223>.
16. Choy KT, Wong AY, Kaewpreedee P, et al. Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro. *Antiviral Res*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32251767>.
17. Vaughn VM, Gandhi T, Petty LA, et al. Empiric antibacterial therapy and community-onset bacterial co-infection in patients hospitalized with COVID-19: a multi-hospital cohort study. *Clin Infect Dis*. 2020; published online ahead of print. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32820807>.
18. Adler H, Ball R, Fisher M, Mortimer K, Vardhan MS. Low rate of bacterial co-infection in patients with COVID-19. *Lancet Microbe*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32835331>.

Appendix A, Table 1. COVID-19 Treatment Guidelines Panel Members

Last Updated: February 11, 2021

Name	Affiliation
Co-Chairs	
Roy M. Gulick, MD, MPH	Weill Cornell Medicine, New York, NY
H. Clifford Lane, MD	National Institutes of Health, Bethesda, MD
Henry Masur, MD	National Institutes of Health, Bethesda, MD
Executive Secretary	
Alice K. Pau, PharmD	National Institutes of Health, Bethesda, MD
Members	
Judith Aberg, MD	Icahn School of Medicine at Mount Sinai, New York, NY
Adaora Adimora, MD, MPH	University of North Carolina School of Medicine, Chapel Hill, NC
Jason Baker, MD, MS	Hennepin Healthcare/University of Minnesota, Minneapolis, MN
Lisa Baumann Kreuziger, MD, MS	Versiti/Medical College of Wisconsin, Milwaukee, WI
Roger Bedimo, MD, MS	University of Texas Southwestern/Veterans Affairs North Texas Health Care System, Dallas, TX
Pamela S. Belperio, PharmD	Department of Veterans Affairs, Los Angeles, CA
Stephen V. Cantrill, MD	Denver Health, Denver, CO
Craig Coopersmith, MD	Emory University School of Medicine, Atlanta, GA
Eric Daar, MD	Harbor-UCLA Medical Center, Torrance, CA
Susan L. Davis, PharmD	Wayne State University School of Pharmacy, Detroit, MI
Amy L. Dzierba, PharmD	New York-Presbyterian Hospital, New York, NY
Laura Evans, MD, MSc	University of Washington, Seattle, WA
John J. Gallagher, DNP, RN	University of Pittsburgh Medical Center, Pittsburgh, PA
Rajesh Gandhi, MD	Massachusetts General Hospital/Harvard Medical School, Boston, MA
David V. Glidden, PhD	University of California San Francisco, San Francisco, CA
Birgit Grund, PhD	University of Minnesota, Minneapolis, MN
Erica J. Hardy, MD, MMSc	Warren Alpert Medical School of Brown University, Providence, RI
Carl Hinkson, MSRC	Providence Health & Services, Everett, WA
Brenna L. Hughes, MD, MSc	Duke University School of Medicine, Durham, NC
Steven Johnson, MD	University of Colorado School of Medicine, Aurora, CO
Marla J. Keller, MD	Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY
Arthur Kim, MD	Massachusetts General Hospital/Harvard Medical School, Boston, MA
Jeffrey L. Lennox, MD	Emory University School of Medicine, Atlanta, GA
Mitchell M. Levy, MD	Warren Alpert Medical School of Brown University, Providence, RI
Gregory Martin, MD, MSc	Emory University School of Medicine, Atlanta, GA
Susanna Naggie, MD, MHS	Duke University School of Medicine, Durham, NC

Name	Affiliation
Members, continued	
Andrew T. Pavia, MD	University of Utah School of Medicine, Salt Lake City, UT
Nitin Seam, MD	National Institutes of Health, Bethesda, MD
Steven Q. Simpson, MD	University of Kansas Medical Center, Kansas City, KS
Susan Swindells, MBBS	University of Nebraska Medical Center, Omaha, NE
Pablo Tebas, MD	University of Pennsylvania, Philadelphia, PA
Phyllis Tien, MD, MSc	University of California, San Francisco/San Francisco VA Healthcare System, San Francisco, CA
Alpana A. Waghmare, MD	Seattle Children's Hospital, Seattle, WA
Kevin C. Wilson, MD	Boston University School of Medicine, Boston, MA
Jinoos Yazdany, MD, MPH	University of California, San Francisco, San Francisco, CA
Philip Zachariah, MD, MSc	Columbia University Irving Medical Center, New York, NY
Community Members	
Danielle M. Campbell, MPH	University of California, Los Angeles, Los Angeles, CA
Carly Harrison	LupusChat, New York, NY
Ex Officio Members, U.S. Government Representatives	
Timothy Burgess, MD	Department of Defense, Bethesda, MD
Joseph Francis, MD, MPH	Department of Veterans Affairs, Washington, DC
Virginia Sheikh, MD, MHS	Food and Drug Administration, Silver Spring, MD
Timothy M. Uyeki, MD, MPH	Centers for Disease Control and Prevention, Atlanta, GA
Robert Walker, MD	Biomedical Advanced Research and Development Authority, Washington, DC
U.S. Government Support Team	
Laura Bosque Ortiz, BS	National Institutes of Health, Bethesda, MD
John T. Brooks, MD	Centers for Disease Control and Prevention, Atlanta, GA
Richard T. Davey, Jr., MD	National Institutes of Health, Bethesda, MD
Laurie K. Doepel, BA	National Institutes of Health, Bethesda, MD
Robert W. Eisinger, PhD	National Institutes of Health, Bethesda, MD
Alison Han, MD (Co-Team Coordinator)	National Institutes of Health, Bethesda, MD
Elizabeth S. Higgs, MD, DTM&H, MIA	National Institutes of Health, Bethesda, MD
Martha C. Nason, PhD (Biostatistic Support)	National Institutes of Health, Bethesda, MD
Kanal Singh, MD, MPH (Co-Team Coordinator)	National Institutes of Health, Bethesda, MD
Assistant Executive Secretaries	
Page Crew, PharmD, MPH	National Institutes of Health, Bethesda, MD
Safia Kuriakose, PharmD	Leidos Biomedical Research, Inc., in support of NIAID, Frederick, MD
Andrea M. Lerner, MD, MS	National Institutes of Health, Bethesda, MD

Appendix A, Table 2. COVID-19 Treatment Guidelines Panel Financial Disclosure for Companies Related to COVID-19 Treatment or Diagnostics

Last Updated: February 11, 2021

Reporting Period: October 1, 2019, to September 30, 2020

Panel Member	Financial Disclosure	
	Company	Relationship
Judith Aberg, MD	Atea Pharmaceuticals	Research Support
	Emergent BioSolutions	Research Support
	Gilead Sciences	Research Support
	Pfizer	Research Support
	Regeneron	Research Support
Adaora Adimora, MD, MPH	Gilead Sciences	Research Support
	Merck & Co.	Advisory Board, Consultant
Jason Baker, MD, MS	Gilead Sciences	Research Support
	Humanigen	Research Support
Lisa Baumann Kreuziger, MD, MS	3M	Stockholder, Spouse Is Employee
	Quercegen Pharmaceuticals	Advisory Board for Nonapproved Medications
	Versiti	Employee
Roger Bedimo, MD, MS	Gilead Sciences	Advisory Board
	Merck & Co.	Advisory Board
	ViiV Healthcare	Advisory Board, Research Support
Pamela S. Belperio, PharmD	None	N/A
Laura Bosque Ortiz, BS	None	N/A
John T. Brooks, MD	None	N/A
Timothy Burgess, MD	None	N/A
Danielle M. Campbell, MPH	ViiV Healthcare	Summit Attendee
Stephen V. Cantrill, MD	None	N/A
Craig Coopersmith, MD	None	N/A
Page Crew, PharmD, MPH	None	N/A
Eric Daar, MD	Genentech	Consultant
	Gilead Sciences	Consultant, Research Support
	Merck & Co.	Consultant, Research Support
	ViiV Healthcare	Research Support
Richard T. Davey, Jr., MD	None	N/A
Susan L. Davis, PharmD	Merck & Co.	Honoraria
Laurie K. Doepel, BA	None	N/A
Amy L. Dzierba, PharmD	None	N/A
Robert W. Eisinger, PhD	None	N/A

Panel Member	Financial Disclosure	
	Company	Relationship
Laura Evans, MD, MSc	None	N/A
Joseph Francis, MD, MPH	None	N/A
John J. Gallagher, DNP, RN	Medtronic	Consultant
Rajesh Gandhi, MD	None	N/A
David V. Glidden, PhD	Gilead Sciences	Consultant
	Merck & Co.	Advisory Board
Birgit Grund, PhD	None	N/A
Roy M. Gulick, MD, MPH	None	N/A
Alison Han, MD	None	N/A
Erica J. Hardy, MD, MMSc	None	N/A
Carly Harrison	AstraZeneca	Advisory Board
	Aurinia Pharmaceuticals	Advisory Board, Stockholder
Elizabeth S. Higgs, MD, DTM&H, MIA	None	N/A
Carl Hinkson, MSRC	None	N/A
Brenna L. Hughes, MD, MSc	Merck & Co.	Advisory Board
Steven Johnson, MD	ViiV Healthcare	Advisory Board
Marla J. Keller, MD	None	N/A
Arthur Kim, MD	None	N/A
Safia Kuriakose, PharmD	None	N/A
H. Clifford Lane, MD	None	N/A
Jeffrey L. Lennox, MD	None	N/A
Andrea M. Lerner, MD, MS	None	N/A
Mitchell M. Levy, MD	Inotrem	Research Support
Gregory Martin, MD, MSc	Beckman Coulter	Consultant
	Genentech	Data and Safety Monitoring Board Chair/Member
	Regeneron	Consultant
Henry Masur, MD	None	N/A
Susanna Naggie, MD, MHS	AbbVie	Research Support
	Gilead Sciences	Research Support
	Vir Biotechnology	Advisory Board, Stockholder
Martha C. Nason, PhD	Bristol-Myers Squibb Company	Stockholder
	Medtronic	Stockholder
Alice K. Pau, PharmD	None	N/A
Andrew T. Pavia, MD	GlaxoSmithKline	Consultant (related to influenza)
Nitin Seam, MD	None	N/A
Virginia Sheikh, MD, MHS	None	N/A
Steven Q. Simpson, MD	None	N/A
Kanal Singh, MD, MPH	None	N/A

Panel Member	Financial Disclosure	
	Company	Relationship
Susan Swindells, MBBS	ViiV Healthcare	Research Support
Pablo Tebas, MD	Inovio Pharmaceuticals	Research Support
Phyllis Tien, MD, MSc	Merck & Co.	Research Support
Timothy M. Uyeki, MD, MPH	None	N/A
Alpana A. Waghmare, MD	AlloVir	Research Support
	Ansun BioPharma	Research Support
	Kyorin Pharmaceutical Co.	Advisory Board
Robert Walker, MD	None	N/A
Kevin C. Wilson, MD	None	N/A
Jinoos Yazdany, MD, MPH	AstraZeneca	Consultant, Research Support
	Eli Lilly and Company	Consultant
	Pfizer	Consultant
Philip Zachariah, MD, MSc	Merck & Co.	Research Support