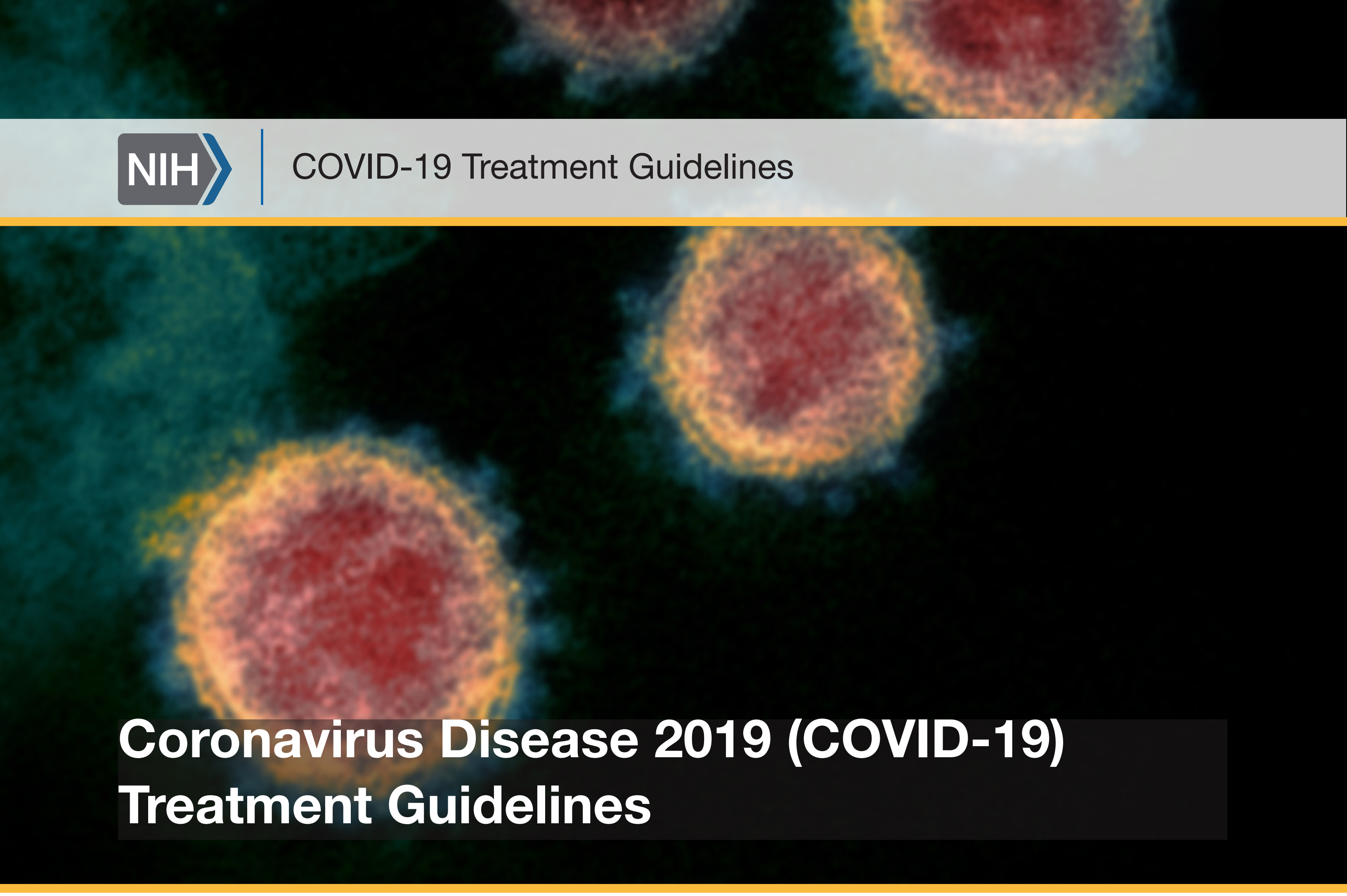
COVID-19 Treatment Guidelines

Coronavirus Disease 2019 (COVID-19) Treatment Guidelines



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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/).

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What's New in the Guidelines

Last Updated: January 14, 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:

January 14, 2021

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

Since the last revision of the Ivermectin section of the Guidelines, results from several randomized clinical trials and retrospective cohort studies of ivermectin use in patients with COVID-19 have been published in peer-reviewed journals or made available as non-peer-reviewed manuscripts. Updates to the Ivermectin section that are underway will include discussion of these studies. Because many of these studies had significant methodological limitations and incomplete information, the Panel cannot draw definitive conclusions about the clinical efficacy of ivermectin for the treatment of COVID-19. As such, the Panel has determined that there are insufficient data 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 further guidance on the role of ivermectin in the treatment of COVID-19.

December 17, 2020

Key Updates to the Guidelines

Clinical Spectrum of SARS-CoV-2 Infection

Formerly: Clinical Presentation of People with SARS-CoV-2 Infection

The Panel expanded the description and discussion of persistent symptoms or organ dysfunction following acute COVID-19 based on the current knowledge of the lingering effects of the disease. The Panel noted that more research and rigorous observational cohort studies are needed to better understand the pathophysiology and clinical course of these postinfectious sequelae and to identify strategies to manage affected patients.

Prevention and Prophylaxis of SARS-CoV-2 Infection

This section was updated with results from two randomized controlled trials that studied the use of hydroxychloroquine as pre-exposure prophylaxis for health care workers exposed to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Antithrombotic Therapy in Patients with COVID-19

This section has been updated based on the most recent literature on venous thromboembolism (VTE) as a complication of COVID-19. The overall recommendations for the use of antithrombotic therapy in outpatient and inpatient settings remain unchanged. The subsection on special considerations during pregnancy and lactation has been updated, including with additional recommendations on the use of antithrombotic therapy in patients with COVID-19 during pregnancy and labor and delivery. The following recommendations have been added to this section:

- For pregnant patients hospitalized for severe COVID-19, prophylactic dose anticoagulation is recommended if there are no contraindications to its use **(BIII)**.
- As for nonpregnant patients, VTE prophylaxis after hospital discharge **is not recommended** for pregnant patients **(AIII)**. Decisions to continue VTE prophylaxis in the pregnant or postpartum patient 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)**.

In addition, the Laboratory Diagnosis subsection of the Critical Care section has been removed. The information in the section was added to Testing for SARS-CoV-2 Infection.

Additional updates to the Guidelines will be forthcoming in January 2021.

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

Last Updated: January 14, 2021

Recommendation

- The COVID-19 Treatment Guidelines Panel (the Panel) has determined that currently there are insufficient data 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 for the treatment of COVID-19.

Rationale

Ivermectin is an antiparasitic drug that is approved by the Food and Drug Administration (FDA) for the treatment of onchocerciasis and strongyloidiasis. Ivermectin is not FDA-approved for the treatment of any viral infection. In general, the drug is well tolerated. It is currently being evaluated as a potential treatment for COVID-19.

Antiviral and Anti-Inflammatory Effects of Ivermectin

Reports from in vitro studies suggest that ivermectin acts by inhibiting the host importin alfa/beta-1 nuclear transport proteins, which are part of a key intracellular transport process that viruses hijack to enhance infection by suppressing the host antiviral response.[1,2] In addition, ivermectin docking in vitro may interfere with the attachment of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein to the human cell membrane.[3]

Ivermectin has been shown to inhibit the replication of SARS-CoV-2 in cell culture. However, pharmacokinetic and pharmacodynamic studies suggest that ivermectin doses up to 100-fold higher than those approved for use in humans would be required to achieve the plasma concentrations necessary to duplicate the drug's antiviral efficacy in vitro.[4,5] Even though ivermectin appears to accumulate in lung tissue, with the doses used in most clinical trials, 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.[6,7]

Ivermectin demonstrates potential anti-inflammatory properties in some in vitro studies,[8,9] properties which have been postulated to be beneficial in the treatment of COVID-19.[10]

Clinical Data

Since the last revision of the Ivermectin 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 made available as preliminary, non-peer-reviewed reports. Some clinical studies showed no benefits or worsening of disease after ivermectin use,[11-14] whereas others reported shorter time to resolution of disease manifestations attributed to COVID-19,[15-18] greater reduction in inflammatory markers,[16,17] shorter time to viral clearance,[11,16] or lower mortality rates in patients who received ivermectin than in patients who received comparator drugs or placebo.[11,16,18]

However, most of the studies reported to date had incomplete information and significant methodological limitations, which make it difficult to exclude common causes of bias. The missing information and limitations include the following:

- 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.
- In addition to ivermectin or the comparator drug, patients also received various concomitant medications (e.g., doxycycline, hydroxychloroquine, azithromycin, zinc, corticosteroids), confounding assessment of the true 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.

Because of these limitations, the Panel cannot draw definitive conclusions about the clinical efficacy or safety 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 for the treatment of COVID-19.

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The COVID-19 Treatment Guidelines Panel's Statement on the Emergency Use Authorization of Baricitinib for the Treatment of COVID-19

Last Updated: December 14, 2020

Baricitinib is an oral Janus kinase (JAK) inhibitor that is selective for JAK1 and JAK2. It is being evaluated for the treatment of COVID-19 because it may prevent cellular immune activation and inflammation. Baricitinib is approved by the Food and Drug Administration (FDA) to treat moderate to severe rheumatoid arthritis. On November 19, 2020, the 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).[1,2]

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

The COVID-19 Treatment Guidelines Panel (the Panel) has reviewed the evidence that was used to support the EUA. The Panel's recommendations for baricitinib are primarily based on findings from the Adaptive COVID-19 Treatment Trial 2 (ACTT-2). However, the Panel also considered the results of the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial. Like ACTT-2, the RECOVERY trial included patients with COVID-19 who required supplemental oxygen at enrollment. The RECOVERY trial reported that dexamethasone conferred a survival benefit among these patients (see Therapeutic Management of Patients With COVID-19).[3]

Each of the Panel's recommendations is assigned two ratings according to the scheme presented at the end of this statement.

After reviewing the available evidence for baricitinib, the Panel has determined the following:

- There are insufficient data for 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 in cases where corticosteroids can be used instead.
- In the rare circumstances where corticosteroids cannot be used, the Panel recommends using baricitinib in combination with remdesivir for the treatment of COVID-19 in hospitalized, nonintubated patients who require oxygen supplementation **(BIIa)**.
- The Panel **recommends against** the use of baricitinib in the absence of 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. Since both agents are potent immunosuppressants, there is potential for an additive risk of infection.
- More data are needed to clarify the role of baricitinib in the management of COVID-19, especially data from randomized trials that compare the use of baricitinib with the current standard of care and evaluate which subpopulations benefit the most from baricitinib. Health care providers are encouraged to discuss participation in baricitinib clinical trials with their patients.

Clinical Trial Data

The Panel's recommendations for baricitinib are largely based on data from ACTT-2, a multinational, randomized, placebo-controlled trial.[4] This trial included 1,033 hospitalized patients with COVID-19 and evidence of pneumonia. Participants were randomized 1:1 to receive baricitinib 4 mg orally or placebo for up to 14 days (or until hospital discharge); both groups of participants also received intravenous remdesivir for 10 days (or until hospital discharge).

The primary endpoint was time to recovery, which was defined as reaching category 1, 2, or 3 on an 8-point ordinal scale during the first 28 days. Patients were excluded from the trial if they were receiving any medications that were used off-label for the treatment of COVID-19, including corticosteroids. During the study, 10.9% of patients in the baricitinib plus remdesivir group and 12.9% of those in the placebo plus remdesivir group received corticosteroids. The median time to recovery was shorter in the baricitinib plus remdesivir group (7 days) than in the placebo plus remdesivir group (8 days) in the overall cohort (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, the largest difference in time to recovery occurred between the baricitinib group (10 days) and the placebo group (18 days; rate ratio 1.51; 95% CI, 1.10–2.08). However, the treatment effect within this subgroup should be interpreted with caution. It was not possible to estimate the median time to recovery within the first 28 days for patients who were on invasive mechanical ventilation or ECMO at study entry. 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). Serious adverse events were less frequent in the baricitinib arm than in the placebo arm (16.0% vs. 21.0%; between-group difference of -5.0 percentage points, 95% CI, -9.8 to -0.3; *P* = 0.03). New infections also occurred less frequently in the baricitinib arm (5.9% vs. 11.2%; between-group difference of -5.3 percentage points, 95% CI, -8.7 to -1.9; *P* = 0.003).

Recommendation Rating Scheme
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

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The COVID-19 Treatment Guidelines Panel's Statement on the Emergency Use Authorization of the Casirivimab Plus Imdevimab Combination for the Treatment of COVID-19

Last Updated: December 2, 2020

Casirivimab (previously REGN10933) and imdevimab (previously REGN10987) are two recombinant human monoclonal antibodies that bind to nonoverlapping epitopes of the spike protein receptor-binding domain (RBD) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The casirivimab plus imdevimab combination blocks the binding of the RBD to the host cell and is being evaluated for the treatment of COVID-19.

On November 21, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) to make the casirivimab plus imdevimab combination available for the treatment of nonhospitalized patients with mild to moderate COVID-19 who are at high risk for progressing to severe disease and/or hospitalization (see the specific EUA criteria for use of the combination below).[1] The issuance of an EUA does not constitute FDA approval of a product.

The FDA has also issued an EUA for bamlanivimab, another SARS-CoV-2 neutralizing antibody, for the same patient population. Please see the COVID-19 Treatment Guidelines Panel's (the Panel's) previously issued statement on the bamlanivimab EUA.

The Panel reviewed the clinical trial data included in the EUA as supporting evidence for the use of casirivimab plus imdevimab for the treatment for mild to moderate COVID-19 in nonhospitalized patients.[1]

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

- At this time, there are insufficient data to recommend either for or against the use of casirivimab plus imdevimab for the treatment of outpatients with mild to moderate COVID-19.
- The casirivimab plus imdevimab combination **should not be considered** the standard of care for the treatment of patients with COVID-19.
- Health care providers are encouraged to discuss participation in SARS-CoV-2 neutralizing antibody clinical trials with patients who have mild to moderate COVID-19.
- Given the possibility of a limited supply of the casirivimab plus imdevimab combination, as well as challenges distributing and administering the drugs, patients at highest risk for COVID-19 progression should be prioritized for use of the drugs through the EUA. In addition, efforts should be made to ensure that communities most affected by COVID-19 have equitable access to casirivimab plus imdevimab.
- Casirivimab plus imdevimab should not be withheld from a pregnant individual who has a condition that poses a high risk of progression to severe COVID-19 if the clinician thinks that the potential benefit of the drug combination outweighs potential risk (see the criteria for EUA use of casirivimab plus imdevimab below).
- Patients who are hospitalized for COVID-19 **should not receive** casirivimab plus imdevimab outside of a clinical trial.
- There are currently no comparative data to determine whether there are differences in clinical efficacy or safety between casirivimab plus imdevimab and bamlanivimab.

Clinical Trial Data

The clinical trial data presented below have not yet been published in a medical journal. Results and data from this trial provided supporting evidence for the casirivimab plus imdevimab EUA. The following data are drawn from the FDA EUA.

R10933-10987-COV-2067 is a Phase 1 and 2, randomized, double-blind, placebo-controlled trial conducted at 96 centers in the United States to evaluate the safety and efficacy of casirivimab plus imdevimab for the treatment of mild to moderate COVID-19 in an outpatient setting. Participants received a single intravenous infusion of the casirivimab plus imdevimab combination within 3 days of having a positive SARS-CoV-2 virologic test result. Participants who were hospitalized because of COVID-19 before or at randomization were excluded from the study. According to the EUA, 799 participants were randomized to receive one of two doses of the casirivimab plus imdevimab combination, either the 2,400 mg dose (casirivimab 1,200 mg and imdevimab 1,200 mg) (n = 266) or the 8,000 mg dose (casirivimab 4,000 mg and imdevimab 4,000 mg) (n = 267), or placebo (n = 266).[1]

The median age of the participants at baseline was 42 years (7% were aged ≥65 years); 85% were White, 50% were Hispanic/Latinx, and 9% were Black. Thirty-four percent of the study participants were considered at high risk for progressing to severe COVID-19 and/or hospitalization (as defined by the EUA criteria outlined below). The median duration of symptoms was 3 days.

The prespecified primary endpoint was the time-weighted average change in nasopharyngeal SARS-CoV-2 level from baseline to Day 7, as measured in a modified full analysis set of participants with detectable virus at baseline (n = 665). This change was greater among the overall group of participants who received casirivimab plus imdevimab (i.e., either the 2,400 mg or 8,000 mg dose of the combination) than among the placebo-treated participants (-0.36 $\log_{10}$ copies/mL; $P < 0.0001$).

A prespecified secondary clinical endpoint was a composite of medically attended visits related to COVID-19 including hospitalization or emergency department, urgent care, or physician office/telemedicine visits within 28 days of treatment. The proportion of patients who had medically attended visits related to COVID-19 was lower among the patients treated with casirivimab plus imdevimab (2.8% for the pooled doses) than among the placebo-treated patients (6.5%).[2] A post hoc analysis of hospitalization or emergency department visit within 28 days of treatment found that the proportion of patients in which these events occurred was lower for the individual and pooled doses of casirivimab plus imdevimab than for placebo. However, the number of participants in each group who met this endpoint was small, and the contribution of hospitalization versus emergency department visit is not provided:

- Placebo: 10 of 231 participants (4%)
- Pooled casirivimab plus imdevimab doses: 8 of 434 participants (2%)
  - Casirivimab plus imdevimab 2,400 mg: 4 of 215 participants (2%)
  - Casirivimab plus imdevimab 8,000 mg: 4 of 219 participants (2%)

In a post hoc analysis of participants at higher risk for hospitalization (using the definition of high risk in the EUA, and thus approximating the population that would be recommended for treatment with casirivimab plus imdevimab per the EUA), four of 151 participants (3%) in the pooled casirivimab plus imdevimab arms versus seven of 78 participants (9%) in the placebo group were hospitalized or had emergency department visits.

The median time to symptom improvement was 5 days for participants who received casirivimab plus imdevimab and 6 days for those who received placebo.

The safety profile of casirivimab plus imdevimab at both the low and the high dose was reportedly similar to that of the placebo. According to the EUA, among 799 participants in the R10933-10987-COV-2067 trial who received casirivimab plus imdevimab, four infusion-related reactions of Grade 2 severity or higher were reported in the 8,000 mg casirivimab plus imdevimab arm. In two of the participants, the infusion-related reactions resulted in permanent discontinuation of the infusion. One participant had an anaphylactic reaction that resolved with treatment.

The analysis of the R10933-10987-COV-2067 study suggests a potential clinical benefit of casirivimab plus imdevimab for outpatients with mild to moderate COVID-19. However, the relatively small number of participants in this early phase trial and the low number of hospitalizations or emergency department visits make it difficult to draw definitive conclusions about the clinical benefit of casirivimab plus imdevimab. The Panel believes that more data are needed to assess the impact of casirivimab plus imdevimab on the disease course of COVID-19 in patients with specific characteristics and/or conditions and will update recommendations as more information becomes available.

High-Risk Criteria for Emergency Use Authorization of the Casirivimab Plus Imdevimab Combination

The FDA EUA allows for the use of casirivimab plus imdevimab 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. High-risk individuals 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 ≥85th 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, 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 or a reactive airway or other chronic respiratory disease that requires daily medication for control

- Casirivimab and imdevimab are not authorized for use in patients:
    - Who are hospitalized due to COVID-19; *or*
    - Who require oxygen therapy due to COVID-19; *or*
    - Who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to an underlying non-COVID-19 related-comorbidity.
- Benefit of treatment with casirivimab plus imdevimab has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies, such as casirivimab and imdevimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 who require high-flow oxygen or mechanical ventilation.

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The COVID-19 Treatment Guidelines Panel's Statement on the Emergency Use Authorization of Bamlanivimab for the Treatment of COVID-19

Last Updated: November 18, 2020

Bamlanivimab (also known as LY-CoV555 and LY3819253) is a neutralizing monoclonal antibody that targets the receptor-binding domain of the spike protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Because this drug may block SARS-CoV-2 entry into host cells, it is being evaluated for the treatment of COVID-19.

On November 9, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) to make bamlanivimab available for the treatment of nonhospitalized patients with mild to moderate COVID-19 who are at high risk for progressing to severe disease and/or hospitalization (see the specific EUA criteria for its use below).[1] The issuance of an EUA does not constitute FDA approval of a product. The COVID-19 Treatment Guidelines Panel (the Panel) reviewed the available evidence from the published data on bamlanivimab for the treatment for COVID-19 and the FDA fact sheet that supported the EUA.

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

- At this time, there are insufficient data to recommend either for or against the use of bamlanivimab for the treatment of outpatients with mild to moderate COVID-19.
- Bamlanivimab **should not be considered** the standard of care for the treatment of patients with COVID-19.
- An interim analysis of the BLAZE-1 study, a Phase 2, randomized, placebo-controlled trial, suggested a potential clinical benefit of bamlanivimab for outpatients with mild to moderate COVID-19. However, the relatively small number of participants and the low number of hospitalizations or emergency department visits make it difficult to draw definitive conclusions about the clinical benefit of bamlanivimab.
- More data are needed to assess the impact of bamlanivimab on the disease course of COVID-19 and to identify those people who are most likely to benefit from the drug. Health care providers are encouraged to discuss participation in bamlanivimab clinical trials with their patients.
- Given the possibility of a limited supply of bamlanivimab, as well as challenges distributing and administering the drug, patients at highest risk for COVID-19 progression should be prioritized for use of the drug through the EUA. In addition, efforts should be made to ensure that communities most affected by COVID-19 have equitable access to bamlanivimab.
- Bamlanivimab should not be withheld from a pregnant individual who has a condition that poses a high risk of progression to severe COVID-19, and the clinician thinks that the potential benefit of the drug outweighs potential risk (see the criteria for EUA use of bamlanivimab below).
- Patients who are hospitalized for COVID-19 **should not receive** bamlanivimab outside of a clinical trial.
- The Panel will continue to evaluate emerging clinical data on the use of bamlanivimab for the treatment of outpatients with mild to moderate COVID-19 and anticipates updating these recommendations as more information becomes available.

Clinical Trial Data

The Blocking Viral Attachment and Cell Entry with SARS-CoV-2 Neutralizing Antibodies (BLAZE-1) trial is a randomized, double-blind, placebo-controlled, Phase 2 trial conducted at 41 centers in the United States to evaluate the safety and efficacy of bamlanivimab for the treatment of mild to moderate COVID-19 in an outpatient setting. Participants received a single intravenous infusion of bamlanivimab within 3 days of having a positive SARS-CoV-2 virologic test result. Participants were excluded if they had a saturation of oxygen (SpO_2) ≤93% on room air, respiratory rate ≥30 breaths/minute, or heart rate ≥125 beats/minute. According to a published interim analysis of the trial, a total of 452 participants were randomized to receive one of three doses of bamlanivimab (700 mg, 2,800 mg, or 7,000 mg) or placebo.[2]

Among the study participants, the median age was 45 years (range: 18–86 years) in the pooled bamlanivimab groups and 46 years (range: 18–77 years) in the placebo group. Although 69.6% (215/309) of the participants in the bamlanivimab groups and 66.4% (95/143) in the placebo group reportedly had risk factors for severe COVID-19, the study population included only a small percentage of participants aged >65 years (10.7% [33/309] in the bamlanivimab groups vs. 14.0% [20/143] in the placebo group). The median time from symptom onset to infusion of bamlanivimab or placebo was 4 days across the groups.

The mean decrease in nasopharyngeal SARS-CoV-2 level from baseline to Day 11 (the primary endpoint) was significantly greater among participants who received the 2,800 mg dose of bamlanivimab than among the placebo-treated participants. The decline in viral load was not significantly different between those who received the 700 mg or 7,000 mg dose of bamlanivimab and those who received placebo.

A prespecified secondary endpoint of COVID-19-related hospitalization, emergency department visit, or death within 28 days of treatment was lower in those who received bamlanivimab than in those who received placebo. However, the percentage of participants in each group who met this endpoint was small (no deaths occurred):

- Placebo: 6.3% (9 of 143)
- All bamlanivimab doses: 1.6% (5 of 309)
  - Bamlanivimab 700 mg: 1.0% (1 of 101)
  - Bamlanivimab 2,800 mg: 1.9% (2 of 107)
  - Bamlanivimab 7,000 mg: 2.0% (2 of 101)

In a post hoc analysis of participants at high-risk for progression to severe COVID-19 (defined as aged ≥65 years or having a body mass index [BMI] ≥35), four of 95 participants (4.2%) in the combined bamlanivimab arms versus seven of 48 (14.6%) participants in the placebo group were hospitalized or had emergency department visits.

In a separate analysis of the BLAZE-1 study reported in the EUA of participants at high risk for hospitalization (using an expanded definition that approximates criteria for those who should be treated with bamlanivimab through the EUA), four of 136 (2.9%) participants in the combined bamlanivimab arms versus seven of 69 (10.1%) participants in the placebo group were hospitalized or had emergency department visits. According to this analysis, the median time to symptom improvement was 6 days for participants who received bamlanivimab and 8 days for those who received placebo.

The safety profile of bamlanivimab at all three doses was reportedly similar to that of the placebo. According to the EUA, among 850 participants in ongoing trials who have received bamlanivimab, one anaphylaxis reaction and one serious infusion-related reaction have been reported. The bamlanivimab infusions were discontinued, and with treatment, both events were resolved.

A substudy of the A Multicenter, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients With COVID-19 (ACTIV-3) trial randomized patients hospitalized with COVID-19 to bamlanivimab or placebo, each in addition to remdesivir. On October 26, 2020, enrollment into this bamlanivimab substudy was stopped due to lack of clinical benefit in hospitalized patients.[3]

High-Risk Criteria for Emergency Use Authorization of Bamlanivimab

The FDA EUA allows for the use of bamlanivimab for the treatment of nonhospitalized adults and children aged ≥12 years and weighing ≥40 kg who have a high risk for progressing to severe COVID-19 or hospitalization. High risks specified in the EUA are:

- Individuals aged ≥12 years who have one of the following conditions:
  - BMI ≥35
  - Chronic kidney disease
  - Diabetes mellitus
  - Immunosuppressive disease
  - Currently receiving immunosuppressive treatment
- Individuals aged ≥65 years
- Individuals aged ≥55 years who have:
  - Cardiovascular disease, *or*
  - Hypertension, *or*
  - Chronic obstructive pulmonary disease/other chronic respiratory disease
- Individuals aged 12 to 17 years who have:
  - BMI ≥85th 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, 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 or a reactive airway or other chronic respiratory disease that requires daily medication for control.

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Introduction

Last Updated: November 3, 2020

The COVID-19 Treatment Guidelines have been developed to inform clinicians 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.

The recommendations in these Guidelines are based on scientific evidence and expert opinion. Each recommendation includes two ratings: a letter (**A**, **B**, or **C**) that indicates the strength of the recommendation and a Roman numeral (**I**, **II**, or **III**) that indicates the quality of the evidence that supports the recommendation (see Table 1).

Panel Composition

Members of the COVID-19 Treatment Guidelines Panel (the Panel) were 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 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 this document.

The names, affiliations, and financial disclosures of the Panel members and ex officio members, as well as members of the 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 must be endorsed by a majority of Panel members. 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 include, but are not limited to, the source of the data, the type of study (e.g., case series, prospective or retrospective cohorts, randomized controlled trial), the quality and suitability of the methods, the number of participants, and the effect sizes observed. Each recommendation is assigned two ratings according to the scheme presented in Table 1.

Table 1. Recommendation Rating Scheme

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement **B:** Moderate recommendation for the statement **C:** Optional recommendation for the statement	**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

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 evolving personal 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 clinical or virologic efficacy 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 not a recommendation; it is used in cases when there are insufficient data to make a recommendation.
- **The Panel recommends against the use of [blank] for the treatment of COVID-19, except in a clinical trial (rating).** This recommendation is 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 COVID-19. There is an array of drugs approved for other indications, as well as multiple investigational agents, that are being studied for the treatment of COVID-19 in clinical trials around the globe. These trials can be accessed at *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 includes drugs that have been approved or licensed for other indications. 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 such trials are still seeking guidance about whether to use these agents.

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 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] ≤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.

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Testing for SARS-CoV-2 Infection

Last Updated: December 17, 2020

Summary Recommendations

• The COVID-19 Treatment Guidelines Panel (the Panel) recommends using a nucleic acid amplification test (NAAT) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on a sample collected from the upper respiratory tract (i.e., nasopharyngeal, nasal, or oropharyngeal specimen) to diagnose acute infection **(AIII)**.
• For intubated and mechanically ventilated adults who are suspected to have COVID-19 but who do not have a confirmed diagnosis:
  • The Panel recommends obtaining lower respiratory tract samples to establish a diagnosis of COVID-19 if an initial upper respiratory sample is negative **(BII)**.
  • The Panel recommends obtaining endotracheal aspirates rather than bronchial wash or bronchoalveolar lavage samples when obtaining lower respiratory samples to establish a diagnosis of COVID-19 **(BII)**.
• The Panel **recommends against** the use of serologic testing as the sole basis for diagnosis of acute SARS-CoV-2 infection **(AIII)**.
• The Panel **recommends against** the use of serologic testing to determine whether a person is immune to SARS-CoV-2 infection **(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

Testing to diagnose severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (i.e., using a nucleic acid amplification test [NAAT] or an antigen test to detect SARS-CoV-2) should be done for all persons who have symptoms that are consistent with COVID-19 and for people who are known to have high-risk exposures to SARS-CoV-2. Ideally, diagnostic testing should also be performed for people who are likely to be at repeated risk of exposure, such as health care workers and first responders. Testing should be considered for individuals who spend time in environments with high population densities (e.g., those who work at or attend a school in person, those who work in the food industry) and for persons after they travel. Testing requirements may vary by state, local, and employer policies. For individuals who are planning to travel, documentation of a recent negative test result may be required to enter some states or countries; in some cases, the documentation may be an acceptable alternative to a period of quarantine upon arrival.

The Food and Drug Administration (FDA) has issued emergency use authorizations (EUAs) for a number of SARS-CoV-2 diagnostic tests (e.g., NAATs, antigen tests),[1] but currently there are no FDA-approved diagnostic tests.

Although nasopharyngeal specimens remain the current standard 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; however, 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. Other sample types, including stool samples, are 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). 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. Due to the high specificity of NAAT, there is no need to obtain a lower respiratory tract sample to diagnose COVID-19 when a patient with recent onset of COVID-19-compatible symptoms has a positive NAAT on an upper respiratory sample. Because the viral load is higher in the lower respiratory tract than in the upper respiratory tract of patients with COVID-19, severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS), more positive results are reported for lower respiratory tract specimens.[4-10] In intubated or mechanically ventilated patients who have clinical signs and symptoms consistent with COVID-19 pneumonia and an initial negative result on an upper respiratory tract sample, a NAAT of a lower respiratory tract sample is recommended **(BII)**. The COVID-19 Treatment Guidelines Panel (the Panel) recommends obtaining endotracheal aspirates rather than bronchial wash or bronchoalveolar lavage (BAL) samples when collecting lower respiratory samples to establish a diagnosis of COVID-19 **(BII)**.

BAL and sputum induction are aerosol-generating procedures that should be performed only with careful consideration of the risk of aerosol generation to staff. Endotracheal aspiration appears to carry a lower risk of aerosolization than BAL, and in the view of some experts, the sensitivity and specificity of endotracheal aspirates and BAL specimens are comparable.

Antigen Testing for SARS-CoV-2 Infection

When compared with RT-PCR-based tests, antigen-based diagnostic tests (which detect viral antigens) are less sensitive but have a 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. When a person who is strongly suspected of having SARS-CoV-2 infection receives a negative result on an initial antigen test, repeat testing using a NAAT should be considered. Advantages of antigen-based tests are their low cost and rapid turnaround. The availability of immediate results makes antigen-based tests 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. Currently, there are limited data to guide the use of rapid antigen 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.[11]

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 are intended to identify persons with recent or prior SARS-CoV-2 infection. Because it may take 21 days or longer after symptom onset for seroconversion or detection of immunoglobulin (Ig) M and/or IgG antibodies to SARS-CoV-2,[12-17] the Panel **does not recommend** the use of serologic testing as the sole basis for diagnosing acute SARS-CoV-2 infection **(AIII)**. Given that 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 serology 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 Centers for Disease Control and Prevention, and the FDA, provide guidance for clinicians regarding the use of serologic testing for SARS-CoV-2.

Several factors should be considered when using these tests, 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.
- 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 antibodies are detected, the results should be interpreted with caution for the following reasons:

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

In communities where the prevalence of SARS-CoV-2 infection is low, the proportion of false positives among all positive test results may be quite high. In these situations, confirmatory testing using another 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:

- Determine who may be eligible to donate convalescent plasma;
- Measure the immune response in SARS-CoV-2 vaccine studies; *and*
- Estimate the proportion of the population exposed to SARS-CoV-2.

Serologic tests **should not be used** to:

- Determine how to separate persons in congregate settings (e.g., schools, dormitories, correctional facilities) based on SARS-CoV-2 status; *or*
- Determine whether persons should return to the workplace.

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Prevention and Prophylaxis of SARS-CoV-2 Infection

Last Updated: December 17, 2020

Summary Recommendations
• The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of any agents 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 any agents for SARS-CoV-2 post-exposure prophylaxis (PEP), except in a clinical trial **(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

General Prevention Measures

Transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is thought to mainly occur through respiratory droplets transmitted from an infectious person to those within 6 feet of the person. Less commonly, airborne transmission of small droplets and particles of SARS-CoV-2 that are suspended in the air can result in transmission to those who are more than 6 feet from an infectious individual. Although rare, infection through this route of transmission can also occur in persons who pass through a room that was previously inhabited by an infectious person. SARS-CoV-2 infection via airborne transmission of small particles tends to occur after prolonged exposure (>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 6 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 is also effective in reducing 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.[3]

Vaccines

Vaccines for SARS-CoV-2 are aggressively being pursued. Vaccine development is typically a lengthy process, often requiring multiple candidates before one proves to be safe and effective. To address the current pandemic, several platforms are being used to develop candidate vaccines for Phase 1 and 2 trials; those that show promise are rapidly moving into Phase 3 trials. Several standard platforms, such as inactivated vaccines, live-attenuated vaccines, and protein subunit vaccines, are being pursued. Some novel approaches are being investigated, including DNA-based and RNA-based strategies and replicating and nonreplicating vector strategies, with the hope of identifying a safe and effective SARS-CoV-2 vaccine that can be used in the near future.[4,5] Phase 3 clinical trial data are available for two candidate vaccines. The Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for one of the vaccines and is discussing a possible EUA for the other vaccine.

Pre-Exposure Prophylaxis

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of any agents 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, 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 for the latest information.

Clinical Trial Data

Hydroxychloroquine

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.[6]

Study Population

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

Results

- The study was based on an assumption of 10% infection rate for the planned inclusion of 100 participants per arm.
- During April 9 to 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 (4 participants [7.4%]) than in the placebo group (2 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%, respectively; $P = 0.04$). 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 in the placebo group (16%).
- There were no cardiac events or 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 and, therefore, the applicability of the study findings to other populations is uncertain.

Interpretation

- There was no clinical benefit of hydroxychloroquine 600 mg per day administered for 8 weeks as PrEP among health care workers 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 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, 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.[7]

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 upon an anticipated 10% event rate of new symptomatic infections. In order to have 80% power, the sample size was determined to be 1,050 participants per arm. However, it became apparent before the first interim analysis that the study would not meet the enrollment target. As a result, and without unblinding, enrollment was stopped. 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.

- Across the groups, there were no significant differences for any of the secondary efficacy endpoints.
- There were significantly more adverse events reported in the once- and twice-weekly hydroxychloroquine arms (31% vs. 36% of participants, respectively; $P < 0.001$ for both groups) than in the placebo group (21% of participants). The most common side effects were stomach upset 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 substantially below the in vitro half-maximal effective concentration (EC_{50}) of hydroxychloroquine. The investigators noted that simulations used to determine the hydroxychloroquine dose for the study predicted drug concentrations that should have been much higher 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 confirmed positive SARS-CoV-2 test results; the remainder had compatible symptoms without a confirmatory diagnosis.

Interpretation

- Hydroxychloroquine 400 mg once- or twice-weekly as PrEP did not reduce documented SARS-CoV-2 infection or symptoms compatible with COVID-19 among health care workers at high risk of infection.
- These findings may suggest that the 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 any agents for SARS-CoV-2 post-exposure prophylaxis (PEP), except in a clinical trial **(AIII)**.

Rationale

At present, there is no known agent that can be administered after exposure to SARS-CoV-2 infection (i.e., as PEP) to prevent infection. Potential options for SARS-CoV-2 PEP that are currently under investigation include chloroquine, hydroxychloroquine, lopinavir/ritonavir, nitazoxanide, vitamin super B-complex, and vitamin D. Other post-exposure preventive strategies that are in development include the use of SARS-CoV-2 monoclonal antibodies and convalescent plasma. Please check *ClinicalTrials.gov* for the latest information.

Clinical Trial Data

Hydroxychloroquine

Both chloroquine and hydroxychloroquine have in vitro activity against severe acute respiratory syndrome-associated coronavirus (SARS-CoV) and SARS-CoV-2.[8,9] A small cohort study without a control group has suggested that hydroxychloroquine might reduce the risk of SARS-CoV-2 transmission to close contacts.[10]

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.[11]

Study Population

- Participants had a high risk 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 6 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), and 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, confirmed by a SARS-CoV-2 positive molecular test or, if testing was not available, by 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%, respectively; $P = 0.35$).
- 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 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, they 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.[12] 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 either 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 illness with at least one of the following symptoms: fever, cough, difficulty breathing, myalgia, headache, sore throat, new olfactory and taste disorders, or diarrhea; and a positive SARS-CoV-2 PCR test. A secondary outcome was onset of SARS-CoV-2 infection defined as either a SARS-CoV-2 PCR positive test or the presence of any of the symptoms compatible with COVID-19. Additional secondary outcomes were development of serological positivity at Day 14 and safety up to 28 days from treatment initiation.

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 2 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 coexisting disease, 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%, respectively; 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 and 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, including gastrointestinal events, nervous system disorders, myalgia, fatigue, or 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 exposed to a PCR-positive case.

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Clinical Spectrum of SARS-CoV-2 Infection

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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) ≥94% on room air at sea level.
- *Severe Illness:* Individuals who have SpO_2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/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 SpO_2 ≥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 SpO_2 <94% on room air at sea level, a respiratory rate of >30 breaths/min, PaO_2/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*.

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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) **(AII)**. • 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 **(CIII)**. **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 **(BII)**. • For the acute resuscitation of adults with COVID-19 and shock, the Panel recommends using buffered/balanced crystalloids over unbalanced crystalloids **(BII)**. • For the acute resuscitation of adults with COVID-19 and shock, the Panel **recommends against** the initial use of albumin for resuscitation **(BI)**. • The Panel **recommends against** using hydroxyethyl starches for intravascular volume replacement in patients with sepsis or septic shock **(AI)**. • The Panel recommends norepinephrine as the first-choice vasopressor **(AII)**. The Panel recommends adding either vasopressin (up to 0.03 units/min) **(BII)** or epinephrine **(CII)** to norepinephrine to raise mean arterial pressure to target or adding vasopressin (up to 0.03 units/min) **(CII)** to decrease norepinephrine dosage. • When norepinephrine is available, the Panel **recommends against** using dopamine for patients with COVID-19 and shock **(AI)**. • The Panel **recommends against** using low-dose dopamine for renal protection **(BII)**. • 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 **(BII)**. • 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 **(BII)**. **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) **(BI)**. • 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 **(BIII)**. • 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 **(CIII)**.

- 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 **(AII)**.
- 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) **(AI)**.
  - The Panel recommends targeting plateau pressures of <30 cm H_2O **(AII)**.
  - The Panel recommends using a conservative fluid strategy over a liberal fluid strategy **(BII)**.
  - The Panel **recommends against** the routine use of inhaled nitric oxide **(AI)**.
- 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 **(BII)**.
  - 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 **(BII)**.
- 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 **(BIII)**.
  - 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 **(CII)**.
  - If recruitment maneuvers are used, the Panel **recommends against** using staircase (incremental PEEP) recruitment maneuvers **(AII)**.
  - 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 with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion

General Considerations

Last Updated: December 17, 2020

Severe cases of COVID-19 may be associated with hypoxemic respiratory failure, acute respiratory distress syndrome, 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, taking special precautions to prevent environmental contamination by SARS-CoV-2 is 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. 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.

Septic Shock and the Inflammatory Response Due to COVID-19

Patients with COVID-19 may express high levels of an array of inflammatory cytokines, often in the setting of deteriorating hemodynamic or respiratory status. This is often referred to as “cytokine release syndrome” or “cytokine storm,” although these are imprecise terms. Intensivists need to consider the full differential diagnosis of shock to exclude other treatable causes of shock (e.g., bacterial sepsis due to pulmonary or extrapulmonary sources, hypovolemic shock due to a gastrointestinal hemorrhage that is unrelated to COVID-19, cardiac dysfunction related to COVID-19 or comorbid atherosclerotic disease, stress-related adrenal insufficiency).

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.[4,6,9-12] COVID-19 may be associated with an array of cardiovascular complications, including acute coronary syndrome, myocarditis, arrythmias, and thromboembolic disease.[13]

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.[14-16] Autopsy studies provide additional evidence of both thromboembolic disease and microvascular thrombosis in patients with COVID-19.[17] Some authors have called for routine surveillance of ICU patients for venous thromboembolism.[18] 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, continuous renal replacement therapy was needed in more than 15% of cases of critical disease.[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.[19-24] The risk factors for severe COVID-19 in children have not yet been established. Data from studies of adults 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 disease.

A new syndrome, multisystem inflammatory syndrome in children (MIS-C), which appears to be a postinfectious complication, has been described.[25,26] 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.[27,28] 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.[29,30]

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.[31] 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.[32] 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.[33] Neurological complications are associated with older age and underlying conditions such as hypertension and diabetes mellitus.[34] Autopsy studies have reported both macrovascular and microvascular thrombosis, with evidence of hypoxic ischemia.[35] 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.[36] 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.[37-39] Cognitive dysfunction affects 30% to 80% of patients discharged from the ICU.[40-42] About 50% of ICU survivors do not return to work within 1 year after discharge.[43] 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.[44]

Early reports suggest that some patients with COVID-19 who have been treated in the ICU express manifestations of PICS.[45] 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.

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Infection Control

Last Updated: October 9, 2020

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

Recommendation

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

Rationale

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

- 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 **(CIII)**.

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.

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Hemodynamics

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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 **(BII)**.

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 **(BII)**.

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 **(BI)**.

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 **(AI)**.
- The Panel recommends norepinephrine as the first-choice vasopressor **(AII)**. The Panel recommends adding either vasopressin (up to 0.03 units/minute) **(BII)** or epinephrine **(CII)** to norepinephrine to raise mean arterial pressure to target or adding vasopressin (up to 0.03 units/minute) **(CII)** to decrease norepinephrine dosage.
- When norepinephrine is available, the Panel **recommends against** using dopamine for patients with COVID-19 and shock **(AI)**.
- The Panel **recommends against** using low-dose dopamine for renal protection **(BII)**.
- 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 **(BII)**.
- 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 **(BII)**.
- 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.

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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) **(BI)**.
- 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 **(BIII)**.
- 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 **(CIII)**.
- 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 **(AII)**.

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 ≥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 (PaO_2/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 (PaO_2/FiO_2 181 mm Hg in supine position vs. PaO_2/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 (PaO_2/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) **(AI)**.
- The Panel recommends targeting plateau pressures of <30 cm H_2O **(AII)**.
- The Panel recommends using a conservative fluid strategy over a liberal fluid strategy **(BII)**.
- The Panel **recommends against** the routine use of inhaled nitric oxide **(AI)**.

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 **(BII)**.
- 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 **(BII)**.

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 (PaO_2/FiO_2 100–200 mm Hg) and severe ARDS (PaO_2/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 **(BIII)**.
- 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 **(CII)**.
- If recruitment maneuvers are used, the Panel **recommends against** using staircase (incremental PEEP) recruitment maneuvers **(AII)**.
- 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.

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Acute Kidney Injury and Renal Replacement Therapy

Last Updated: December 17, 2020

Recommendations

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

Rationale

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

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

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

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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 Immune-Based Therapy 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 regarding adjunctive therapy used in the critical care setting, including antithrombotic therapy and vitamin C, can be found in the Adjunctive Therapy section.

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 EMCO 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*

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Therapeutic Management of Patients with COVID-19

Last Updated: December 3, 2020

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 anti-SARS-CoV-2 monoclonal antibodies bamlanivimab and casirivimab plus imdevimab are available through Emergency Use Authorizations for outpatients who are at high risk for disease progression.

Remdesivir, an antiviral agent, is currently the only drug that is approved by the Food and Drug Administration 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. A comprehensive summary of the clinical data for the drugs that are being investigated for the treatment of COVID-19 can be found in the Antiviral Therapy, Immune-Based Therapy, and Adjunctive Therapy sections of these Guidelines.

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
Not Hospitalized, Mild to Moderate COVID-19	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] These EUAs do not authorize use in hospitalized patients. **Dexamethasone** should not be used **(AIII)**.
Hospitalized[a] But Does Not Require Supplemental Oxygen	**Dexamethasone** should not be used **(AIIa)**. 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.
Hospitalized[a] and Requires Supplemental Oxygen (But Does Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO)	Use one of the following options: • **Remdesivir**[b,c] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone**[d] **plus remdesivir**[b,c] (e.g., for patients who require increasing amounts of supplemental oxygen) **(BIII)**[e,f] • **Dexamethasone**[d] (e.g., when combination therapy with remdesivir cannot be used or is not available) **(BI)**
Hospitalized[a] and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	Use one of the following options: • **Dexamethasone**[d,f] **(AI)** • **Dexamethasone**[d] **plus remdesivir**[b,c] **(BIII)**[e,f]
Hospitalized[a] and Requires Invasive Mechanical Ventilation or ECMO	**Dexamethasone**[d] **(AI)**[g]

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

[a] See the Panel's statements on the FDA EUAs for bamlanivimab and casirivimab plus imdevimab. These EUAs do not authorize use in hospitalized patients.
[b] The remdesivir dose is 200 mg IV for one dose, followed by 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.
[c] 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.
[d] 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, such as prednisone, methylprednisolone, or hydrocortisone, may be used. See the Corticosteroids section for more information.
[e] The combination of dexamethasone and remdesivir has not been studied in clinical trials.
[f] 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.
[g] The combination of dexamethasone and remdesivir may be considered for patients who have recently been intubated **(CIII)**. Remdesivir alone **is not recommended**.

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

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

Last Updated: November 3, 2020

Summary Recommendations
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 2. **Remdesivir** • See Therapeutic Management of Patients with COVID-19 for recommendations on using remdesivir with or without dexamethasone. **Chloroquine or Hydroxychloroquine With or Without Azithromycin** • 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 **(AI)**. • The Panel **recommends against** the use of **high-dose chloroquine** (600 mg twice daily for 10 days) for the treatment of COVID-19 **(AI)**. **Lopinavir/Ritonavir and Other HIV Protease Inhibitors** • The Panel **recommends against** using **lopinavir/ritonavir (AI)** or **other HIV protease inhibitors (AIII)** to treat COVID-19, except in a clinical trial. **Ivermectin** • The Panel **recommends against** the use of **ivermectin** for the treatment of COVID-19, except in a clinical trial **(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

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 into 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 antivirals 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 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.

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Remdesivir

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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 Remdesivir: Selected Clinical Data 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 2: Characteristics of Antiviral Agents That Are Approved or Under Evaluation for Treatment of COVID-19 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.

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Remdesivir: Selected Clinical Data

Last Updated: November 3, 2020

Remdesivir is approved by the Food and Drug Administration for the treatment of COVID-19 in hospitalized adult and pediatric patients (aged ≥12 years and weighing ≥40 kg).[1]

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* for more information on clinical trials that are evaluating remdesivir.

Multinational Randomized Controlled Trial of Remdesivir Versus Placebo in Hospitalized Patients

The Adaptive COVID-19 Treatment Trial (ACTT-1) is a National Institutes of Health-sponsored, multinational, randomized, double-blind, placebo-controlled trial.[2] Patients received either placebo for 10 days or intravenous (IV) remdesivir at a dose of 200 mg on Day 1 and then 100 mg daily for up to 9 more days. The primary study endpoint was time to clinical recovery. Severity of illness at baseline and at Day 15 was assessed using an eight-point ordinal scale:

1. Not hospitalized, no limitations
2. Not hospitalized, with limitations
3. Hospitalized, no active medical problems
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 extracorporeal membrane oxygenation (ECMO)
8. Death

Study Population

The study population consisted of hospitalized patients aged ≥18 years with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Patients were enrolled if they met at least one of the following conditions:

- The patient had pulmonary infiltrates, as determined by radiographic imaging;
- SpO_2 was ≤94% on room air;
- The patient required supplemental oxygen;
- The patient was on mechanical ventilation; *or*
- The patient was on ECMO.

The study excluded individuals who had alanine transaminase (ALT) or aspartate transaminase (AST) levels >5 times the upper limit of normal (ULN), those who had an estimated glomerular filtration rate <30 mL/minute, and those who were pregnant or breastfeeding.

Results

- 1,062 participants were enrolled.
- The median time from symptom onset to randomization was 9 days (IQR 6–12 days).

- Remdesivir significantly reduced the time to recovery compared to placebo (median time to recovery was 10 days vs. 15 days; recovery rate ratio 1.29; 95% CI, 1.12–1.49; $P < 0.001$).
- Clinical improvement based on the ordinal scale outlined above was significantly higher at Day 15 in patients who received remdesivir than in those who received placebo (OR 1.5; 95% CI, 1.2–1.9, $P < 0.001$).
- The benefit of remdesivir for reducing time to recovery was clearest in the subgroup of hospitalized patients who required supplemental oxygenation at study enrollment (ordinal scale 5, n = 435; recovery rate ratio 1.45; 95% CI, 1.18–1.79). In a post hoc analysis of deaths by Day 15, remdesivir appeared to confer a survival benefit in this subgroup (HR for death 0.28; 95% CI, 0.12–0.66).
- In patients who required high-flow oxygen or noninvasive ventilation at study enrollment (ordinal scale 6, n = 193), 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 a post hoc analysis of deaths by Day 15, there was no evidence that remdesivir had an impact on the mortality rate in this subgroup (HR 0.82; 95% CI, 0.40–1.69).
- Among the patients who were on mechanical ventilation or ECMO at study enrollment (ordinal scale 7, n = 285), there was no observed difference in time to recovery between the remdesivir and placebo groups (recovery rate ratio 0.98; 95% CI, 0.70–1.36). In a post hoc analysis of deaths by Day 15, there was no evidence that remdesivir had an impact on the mortality rate in this subgroup (HR 0.76; 95% CI, 0.39–1.50).
- Among patients who were classified as having mild to moderate disease at enrollment, there was no difference in the median time to recovery between the remdesivir and placebo groups. Mild to moderate disease was defined as SpO_2 >94% on room air and a respiratory rate of <24 breaths/minute without supplemental oxygen.
- There was no statistically significant difference in mortality by Day 29 between the remdesivir (11.4%) and placebo (15.2%) arms (HR 0.73; 95% CI, 0.52-1.03; $P = 0.07$).
- Mortality rates by Day 29 differed between groups according to baseline severity, with the greatest difference observed in ordinal scale 5 (HR 0.30; 95% CI, 0.14-0.64), compared to ordinal scale 6 (HR 1.02; 95% CI, 0.54-1.91) and ordinal scale 7 (HR 1.13; 95% CI, 0.67-1.89).
- The benefit of remdesivir was greater in participants who were randomized during the first 10 days after symptom onset.
- The percentages of participants with serious adverse effects (AEs) were similar in the remdesivir and placebo groups (25% vs. 32%).
- Transaminase elevations occurred in 6% of remdesivir recipients and 10.7% of placebo recipients.

Limitations

- The study was conducted in patients with a wide range of disease severity. The study was not powered to detect differences within subgroups.
- The study was powered to detect differences in clinical improvement, not mortality.
- No data were collected on longer-term morbidity.

Interpretation

In patients with severe COVID-19, remdesivir reduced the time to clinical recovery. The benefit of remdesivir was most apparent in hospitalized patients who only required supplemental oxygen. There was no observed benefit of remdesivir in those who were on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO, but the study was not powered to detect differences within subgroups. There was no observed benefit of remdesivir in patients with mild or moderate COVID-19, but the number of participants in these categories was relatively small.

Randomized Controlled Trial of Remdesivir Versus Placebo for Severe COVID-19 in China

This was a multicenter, double-blind, randomized, placebo-controlled trial that evaluated patients with severe COVID-19 in China. Patients were randomized 2:1 to receive IV remdesivir (200 mg on Day 1, followed by 100 mg daily) or normal saline placebo for 10 days. The primary study endpoint was time to clinical improvement, defined as improvement on an ordinal scale or discharged alive from the hospital, whichever came first. The planned sample size was 453 patients.[3]

Study Population

This study enrolled hospitalized adults with laboratory-confirmed SARS-CoV-2 infection whose time from symptom onset to randomization was <12 days. These patients had SpO_2 ≤94% on room air or PaO_2/FiO_2 <300 mm Hg and radiographically confirmed pneumonia.

Results

- In this study, 237 patients were randomized to receive remdesivir (n = 158) or placebo (n = 79). The study was stopped before target enrollment was reached due to control of the COVID-19 outbreak in China.
- The median time from symptom onset to randomization was 9 days for the remdesivir group and 10 days for the placebo group.
- Sixty-five percent of the participants in the remdesivir group and 68% of the participants in the placebo group received corticosteroids.
- Twenty-eight percent of the participants in the remdesivir group and 29% of the participants in the placebo group received lopinavir/ritonavir.
- Twenty-nine percent of the participants in the remdesivir arm and 38% of the participants in the placebo arm received interferon alfa-2b.

Study Endpoints

- There was no difference in the time to clinical improvement between the remdesivir and placebo groups (median time to clinical improvement was 21 days vs. 23 days; HR 1.23; 95% CI, 0.87–1.75).
- For patients who started remdesivir or placebo within 10 days of symptom onset, a faster time to clinical improvement was seen in the remdesivir arm than in the placebo arm (median of 18 days vs. 23 days; HR 1.52; 95% CI, 0.95–2.43); however, this was not statistically significant.
- The 28-day mortality was similar for the two study arms (14% of participants in the remdesivir arm vs. 13% in the placebo arm).
- There was no difference between the groups in SARS-CoV-2 viral load at baseline, and the rate of decline over time was similar between the two groups.
- The number of participants who experienced AEs was similar between the two groups (66% of participants in the remdesivir arm vs. 64% in the placebo arm).
- More participants in the remdesivir arm discontinued therapy due to AEs (12% of participants in the remdesivir arm vs. 5% in the placebo arm).

Limitations

- The study was terminated early because it did not reach its target enrollment; as a result, the sample size did not have sufficient power to detect differences in clinical outcomes.
- The use of concomitant medications (i.e., corticosteroids, lopinavir/ritonavir, interferons) may have obscured the effects of remdesivir.

Interpretation

There was no difference in time to clinical improvement, 28-day mortality, or rate of SARS-CoV-2 clearance between remdesivir-treated and placebo-treated patients; however, the study was underpowered to detect differences in these outcomes between the two groups.

Remdesivir Versus Standard Care in Hospitalized Patients with Moderate COVID-19

This open-label, randomized trial compared the use of 10 days of remdesivir (n = 197) or 5 days of remdesivir (n = 199) to "standard care" (n = 200) in hospitalized patients.4 Remdesivir was administered intravenously at a dose of 200 mg on Day 1 and then 100 mg daily.

Study Population

The study enrolled patients with laboratory-confirmed SARS-CoV-2 infection and moderate pneumonia, which was defined as radiographic evidence of pulmonary infiltrates and SpO_2>94% on room air at sea level.

Results

- Demographic characteristics and baseline disease characteristics were similar across the three study groups.
- Patients who received 5 days of remdesivir had significantly higher odds of having a better clinical status distribution on Day 11 than those who received standard care (OR 1.65; 95% CI, 1.09–2.48; *P* = 0.02).
- The clinical status distribution on Day 11 was not significantly different between the patients who received 10 days of remdesivir and those who received standard care (*P* = 0.18).
- By Day 28, there were more hospital discharges among the patients who received remdesivir (89% in the 5-day group and 90% in the 10-day group) than among those who received standard care (83% of patients).
- Mortality was low in all groups (1% to 2%).
- Several AEs occurred more frequently among patients who were treated with remdesivir than among those who received standard care: nausea (10% of patients vs. 3% of patients), hypokalemia (6% vs. 2%), and headache (5% vs. 3%).

Limitations

- The open-label design of this study may have affected decisions related to concomitant medication use and hospital discharge.
- Compared with the remdesivir groups, a greater proportion of participants in the standard care group received hydroxychloroquine, lopinavir/ritonavir, or azithromycin, which may cause AEs and which have not been shown to have a clinical benefit in hospitalized patients with COVID-19.
- The study did not collect data on the time to return to activity for patients who were discharged from the hospital.

Interpretation

Hospitalized patients with moderate COVID-19 who received 5 days of remdesivir had better outcomes than those who received standard care; however, the difference between the groups was of uncertain clinical importance.

Multinational, Randomized Trial of Different Durations of Remdesivir Treatment in Hospitalized Patients

This was a manufacturer-sponsored, multinational, randomized, open-label trial in hospitalized adolescents and adults with COVID-19. Participants were randomized 1:1 to receive either 5 days or 10 days of IV remdesivir (200 mg on Day 1, followed by 100 mg daily). The primary study endpoint was clinical status at Day 14, which was assessed using a seven-point ordinal scale:[5]

1. Death
2. Hospitalized, on invasive mechanical ventilation or ECMO
3. Hospitalized, on noninvasive ventilation or high-flow oxygen devices
4. Hospitalized, requiring low-flow supplemental oxygen
5. Hospitalized, not requiring supplemental oxygen, but requiring ongoing medical care for COVID-19 or for other reasons
6. Hospitalized, not requiring supplemental oxygen or ongoing medical care (other than the care that was specified in the protocol for remdesivir administration)
7. Not hospitalized

Study Population

The study enrolled hospitalized patients aged ≥12 years with confirmed SARS-CoV-2 infection and radiographic evidence of pulmonary infiltrates.

Patients in this study had either SpO_2 ≤94% on room air or were receiving supplemental oxygen. The study excluded patients who were receiving mechanical ventilation or ECMO or who had multiorgan failure, an ALT or AST level >5 times ULN, or an estimated creatinine clearance <50 mL/minute.

Results

- Out of 402 randomized participants, 397 began 5 days (n = 200) or 10 days (n = 197) of remdesivir treatment.
- At baseline, participants in the 10-day group had worse clinical status (based on ordinal scale distribution) than those in the 5-day group ($P = 0.02$).
- After adjusting for imbalances in the baseline clinical status, the Day 14 distribution in clinical status on the ordinal scale was similar in the 5-day and 10-day groups ($P = 0.14$)
- The time to achieve a clinical improvement of at least two levels on the ordinal scale (median day of 50% cumulative incidence) was similar in the 5-day and 10-day groups (10 days vs. 11 days).
- The median durations of hospitalization among patients who were discharged on or before Day 14 were similar in the 5-day group (7 days; IQR 6–10 days) and 10-day group (8 days; IQR 5–10 days).
- Serious AEs were more common in the 10-day group (35%) than in the 5-day group (21%). Four percent of patients in the 5-day group and 10% of patients in the 10-day group stopped treatment because of AEs.

Limitations

- This was an open-label trial without a placebo control group, so the clinical benefit of remdesivir could not be assessed.
- There were baseline imbalances in the clinical status of participants in the 5-day and 10-day groups.

Interpretation

In hospitalized patients with severe COVID-19 who were not on mechanical ventilation or ECMO, remdesivir treatment for 5 or 10 days had similar clinical benefit.

Other Reviewed Studies

The clinical trials described in this section do not represent all of the trials that the Panel reviewed while developing the recommendations for remdesivir. The studies summarized above are those that have had the greatest impact on the Panel's recommendations.

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Chloroquine or Hydroxychloroquine With or Without Azithromycin

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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 **(AI)**.
- 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 Chloroquine or Hydroxychloroquine With or Without Azithromycin: Selected Clinical Data 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 Chloroquine or Hydroxychloroquine With or Without Azithromycin: Selected Clinical Data.

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 Chloroquine or Hydroxychloroquine With or Without Azithromycin: Selected Clinical Data 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 arrythmia, 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.

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Chloroquine or Hydroxychloroquine With or Without Azithromycin: Selected Clinical Data

Last Updated: October 9, 2020

Chloroquine is approved by the Food and Drug Administration (FDA) for the treatment and prevention of malaria and for the treatment of extraintestinal amebiasis. Hydroxychloroquine is approved by the FDA for the treatment of lupus erythematosus, malaria, and rheumatoid arthritis. Azithromycin is commonly used for the treatment and/or prevention of mycobacterial (nontuberculous) infection, sexually transmitted infections, and various bacterial infections. Azithromycin has primarily been studied for the treatment of COVID-19 when it is used in combination with hydroxychloroquine. The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial includes an azithromycin monotherapy arm, which is currently enrolling.

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* for more information on clinical trials that are evaluating chloroquine, hydroxychloroquine, and azithromycin.

Randomized Controlled Trials

The Effect of Hydroxychloroquine in Hospitalized Patients with COVID-19: Preliminary Results from a Multicenter, Randomized Controlled Trial

This study has not been peer reviewed.

RECOVERY is an ongoing, open-label, randomized controlled trial with multiple arms, including a control arm; in one arm, participants received hydroxychloroquine. The trial was conducted across 176 hospitals in the United Kingdom and enrolled hospitalized patients with clinically suspected or laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Patients with prolonged QTc intervals were excluded from the hydroxychloroquine arm.

Patients were randomized in a 2:1 ratio to receive either the usual standard of care only or the usual standard of care plus hydroxychloroquine or one of the other treatments in the platform trial. Patients in the hydroxychloroquine arm received a loading dose of hydroxychloroquine 800 mg at entry and at 6 hours, followed by hydroxychloroquine 400 mg every 12 hours for the next 9 days or until discharge. The primary outcome was all-cause mortality at Day 28 after randomization.

The trial enrollment ended early on June 5, 2020, after an independent data-monitoring committee recommended reviewing the unblinded data, and the investigators and trial-steering committee concluded that the data showed no beneficial effect of hydroxychloroquine.[1]

Patient Characteristics

- Of the 7,513 participants who were eligible for hydroxychloroquine, 1,561 were randomized to receive hydroxychloroquine and 3,155 were randomized to receive standard of care. The remaining participants were randomized to other treatment arms in the study.
- In both the hydroxychloroquine arm and the standard of care arm, the mean ages were 65 years; 41% of the participants were aged ≥70 years.
- Ninety percent of patients had laboratory-confirmed SARS-CoV-2 infection.
- Comorbidities were common; 57% of patients had at least one major comorbidity. Diabetes mellitus was present in 27% of patients, heart disease in 26%, and chronic lung disease in 22%.

- At randomization, 17% of patients were receiving invasive mechanical ventilation or extracorporeal membrane oxygenation, 60% were receiving oxygen only (with or without noninvasive ventilation), and 24% were receiving neither.
- The use of azithromycin or another macrolide during the follow-up period was similar in both arms (17% vs. 19%), as was the use of dexamethasone (8% vs. 9%).

Results

- There was no significant difference in the primary outcome of 28-day mortality between the two arms; 418 patients (26.8%) in the hydroxychloroquine arm and 788 patients (25.0%) in the standard of care arm had died by Day 28 (rate ratio 1.09; 95% CI, 0.96–1.23; *P* = 0.18).
- A similar 28-day mortality for hydroxychloroquine 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.
- Participants in the hydroxychloroquine arm were less likely to survive hospitalization and had a longer median time to discharge than patients in the standard of care arm. In addition, participants who were randomized to receive hydroxychloroquine 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 the hydroxychloroquine arm and 1,357 patients (43.0%) in the standard of care arm. There were no differences between the arms in the frequency of supraventricular tachycardia, ventricular tachycardia or fibrillation, or instances of atrioventricular block that required intervention.

Limitations

- The study was not blinded.
- Information on the occurrence of new major cardiac arrythmia was not collected throughout the entire trial period.

Interpretation

Hydroxychloroquine does 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 were randomized to receive hydroxychloroquine 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 hydroxychloroquine.

Randomized Controlled Trial of Hydroxychloroquine and Hydroxychloroquine Plus Azithromycin Among Hospitalized Patients with Mild or Moderate COVID-19 in Brazil

This study was an open-label, three-arm, randomized controlled trial that was conducted in Brazil. The study enrolled hospitalized patients aged ≥18 years with suspected or confirmed cases of mild or moderate COVID-19 and duration of symptoms ≤14 days.

Patients received either standard of care alone, hydroxychloroquine 400 mg twice daily for 7 days (plus standard of care), or hydroxychloroquine 400 mg twice daily plus azithromycin 500 mg daily for 7 days (plus standard of care). The primary outcome was clinical status at Day 15, as assessed by a seven-point ordinal scale among the patients with confirmed COVID-19 (modified intention to treat analysis). Exclusion criteria included the need for >4 L of supplemental oxygen or ≥40% FiO_2 by face mask, a history of ventricular tachycardia, or a QT interval ≥480 ms. Steroids, other immunomodulators, and antiviral agents were allowed; 23.3% to 23.9% of patients received oseltamivir.[2]

Patient Characteristics

- The analysis included 504 patients with confirmed COVID-19.
- The mean patient age was 50 years, and 58% of patients were men.
- At baseline, 58.2% of patients were ordinal level 3 (hospitalized without oxygen), and 41.8% were ordinal level 4 (hospitalized with oxygen).
- The median time from symptom onset to randomization was 7 days.

Results

- There was no significant difference between the odds of worse clinical status at Day 15 for patients in the hydroxychloroquine group (OR 1.21; 95% CI, 0.69–2.11; *P* = 1.00) and patients in the hydroxychloroquine plus azithromycin group (OR 0.99; 95% CI, 0.57–1.73; *P* = 1.00).
- There were no significant differences in the secondary outcomes of the three 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 who received hydroxychloroquine plus azithromycin (39.3%) or hydroxychloroquine alone (33.7%) experienced adverse events than those who received standard of care (22.6%).
- QT prolongation was more common in patients who received hydroxychloroquine plus azithromycin or hydroxychloroquine alone than in patients who received standard of care alone, but fewer patients in the standard of care alone group had serial electrocardiographic studies performed during the follow-up period.

Limitations

- The study was not blinded.
- The follow-up period was restricted to 15 days.

Interpretation

Neither hydroxychloroquine alone nor hydroxychloroquine plus azithromycin improved clinical outcomes at Day 15 after randomization among hospitalized patients with mild or moderate COVID-19.

Randomized Controlled Trial of Hydroxychloroquine Versus Standard of Care for Mild or Moderate COVID-19

This multicenter, randomized, open-label trial compared hydroxychloroquine 1,200 mg once daily for 3 days followed by hydroxychloroquine 800 mg once daily for the rest of the treatment duration (which was 2 weeks for patients with mild or moderate COVID-19 [99% of the patients] and 3 weeks for two patients with severe disease) to standard of care.[3]

Results

- Each study arm enrolled 75 patients. Patients were randomized at a mean of 16.6 days after symptom onset.
- The hydroxychloroquine arm and the standard of care arm had similar negative polymerase chain reaction (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).
- There was no difference in the probability of symptom alleviation between the groups in the intention-to-treat analysis.

Limitations

- It is unclear how the overall rate of symptom alleviation was calculated.
- The study did not reach the target sample size.

Interpretation

This study demonstrated no difference in the rate of viral clearance between hydroxychloroquine and standard of care.

High-Dose Chloroquine Versus Low-Dose Chloroquine

A randomized, double-blind, Phase 2b study compared two different chloroquine regimens, chloroquine 600 mg twice daily for 10 days (high dose) and chloroquine 450 mg twice daily for 1 day followed by 450 mg for 4 days (low dose), in hospitalized adults with suspected cases of severe COVID-19. All patients also received ceftriaxone plus azithromycin; 89.6% of patients received oseltamivir.[4]

The planned study sample size was 440 participants. The study was stopped by the study's data safety monitoring board after 81 patients were enrolled.

Results

- Forty-one patients were randomized into the high-dose arm and 40 patients were randomized into the low-dose arm.
- The overall fatality rate was 27.2%.
- Mortality by Day 13 was higher in the high-dose arm than in the low-dose arm (death occurred in 16 of 41 patients [39%] vs. in six 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 the high-dose arm (18.9% of patients) than in the low-dose arm (11.1% of patients).
- Two patients in the high-dose arm experienced ventricular tachycardia before death.

Limitations

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.

Interpretation

Despite the small number of patients enrolled, this study raises concerns about an increased risk of mortality when high-dose chloroquine (600 mg twice daily) is administered in combination with azithromycin and oseltamivir.

Randomized Placebo-Controlled Trial of Hydroxychloroquine in Nonhospitalized Adults with Early COVID-19

This randomized, placebo-controlled trial in the United States and Canada enrolled participants with ≤4 days of symptoms that were compatible with COVID-19 and either laboratory-confirmed SARS-CoV-2 infection or high-risk exposure within the previous 14 days. Participants were recruited through internet-based surveys. They were randomized to receive hydroxychloroquine (800 mg once, followed by 600 mg in 6–8 hours, and then 600 mg daily for 4 days) or placebo (with the same dosing frequency).

The planned primary endpoint was ordinal outcome by Day 14 in four categories: not hospitalized, hospitalized, intensive care unit (ICU) stay, or death. Due to lower than expected event rates, a new primary endpoint was defined: change in overall symptom severity over 14 days (assessed on a 10-point, self-reported, visual analog scale). A longitudinal mixed model that was adjusted for baseline severity score was used for the anaylsis.[5]

Patient Characteristics

- Data were collected from 423 participants (212 in the hydroxychloroquine arm and 211 in the placebo arm) for the primary end point.
- Of the 423 participants, 241 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%).
- The median age was 40 years, and 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.
- Fifty-six percent of patients were enrolled on Day 1 of symptom onset.
- In this study, 341 participants (81%) had either a positive PCR result or a high-risk exposure to a PCR-positive contact.

Results

- Compared to the placebo recipients, hydroxychloroquine 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 on hydroxychloroquine and 30% of those in the placebo group at Day 14 ($P = 0.21$).
- There was no difference in the incidence of hospitalization (four patients in the hydroxychloroquine group vs. 10 patients in the placebo group). Two of the 10 placebo participants were hospitalized for reasons that were unrelated to COVID-19.
- A higher percentage of patients who received hydroxychloroquine experienced adverse events (mostly gastrointestinal) than patients who received placebo (43% vs. 22%; $P < 0.001$).

Limitations

- This study enrolled a highly heterogenous participant population. Only 227 of the 423 participants (53.7%) were confirmed PCR-positive for SARS-CoV-2.
- Changing the primary endpoint during the study 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.
- The visual analog scale has not been commonly used, and its ability to assess acute viral respiratory infections in clinical trials has not been validated.

Interpretation

The study has some limitations, and it did not find evidence that early administration of hydroxychloroquine reduced symptom severity in patients with mild COVID-19.

Open-Label Randomized Controlled Trial of Hydroxychloroquine in Nonhospitalized Adults with Mild COVID-19

This open-label randomized controlled trial in Spain enrolled nonhospitalized adults with laboratory-confirmed SARS-CoV-2 infection and <5 days of mild COVID-19 symptoms. Participants were mostly health care workers. They were randomized to receive hydroxychloroquine (800 mg on Day 1, followed by 400 mg once daily for 6 days) or no antiviral treatment (control group). The primary endpoint was reduction in SARS-CoV-2 viral load, which was assessed using nasopharyngeal swabs on Days 3 and 7. Secondary endpoints were disease progression up to Day 28 and time to complete resolution of symptoms.[6]

Patient Characteristics

- Of 353 participants who were randomized into the hydroxychloroquine group or the control group, 60 were excluded from the intention to treat analysis because of negative baseline reverse transcription-PCR (RT-PCR), missing RT-PCR at all follow-up visits, or consent withdrawal.
- The intention to treat analysis included 293 patients (157 in the control group and 139 in the hydroxychloroquine group). Mean age was 41.6 years, and 67% of patients were women.
- The majority of patients were healthcare workers (87%), and 53% reported chronic health conditions.
- The median time from symptom onset to enrollment was 3 days (IQR 2–4 days). The most commonly reported COVID-19 symptoms were fever, cough, and sudden olfactory loss.

Results

- There was no significant difference in viral load reduction between the control group and hydroxychloroquine group at Day 3 (-1.41 vs. -1.41 $\log_{10}$ copies/mL; difference of 0.01; 95% CI, -0.28 to 0.29), or at Day 7 (-3.37 vs. -3.44 $\log_{10}$ copies/mL; difference of -0.07; 95% CI, -0.44 to 0.29).
- There was no difference in the risk of hospitalization between the two groups: 7.1% vs. 5.9% (risk ratio 0.75; 95% CI, 0.32–1.77).
- There was no difference in the median time from randomization to the resolution of COVID-19 symptoms between the two groups (12.0 days in the control arm vs. 10.0 days in the hydroxychloroquine arm; $P = 0.38$).
- A higher percentage of participants in the hydroxychloroquine arm than in the control arm experienced adverse events during the 28-day follow-up period (72% vs. 9%). The most common adverse events were gastrointestinal disorders and "nervous system disorders."
- Serious adverse events were reported in 12 patients in the control group and in eight patients in the hydroxychloroquine group. The serious adverse events that occurred among the hydroxychloroquine patients were not deemed to be related to the drug.

Limitations

- This was an open-label, non-placebo-controlled trial. The study design allowed for the possibility of drop-outs in the control arm and over-reporting of adverse events in the hydroxychloroquine arm.
- There was a change in the intervention during the study; the authors initially planned to include a combination of hydroxychloroquine and darunavir/cobicistat.
- The majority of the participants were relatively young health care workers.

Interpretation

Early administration of hydroxychloroquine to patients with mild COVID-19 disease did not result in improvement in virologic clearance, a lower risk of disease progression, or a reduced time to symptom improvement.

Observational Studies

New York Department of Health Study on Hydroxychloroquine With or Without Azithromycin

A retrospective, multicenter, observational study evaluated the use of hydroxychloroquine with and without azithromycin in a random sample of 1,438 inpatients with COVID-19. Patients were categorized into four treatment groups: hydroxychloroquine plus azithromycin, hydroxychloroquine alone, azithromycin alone, or neither drug. The primary outcome measure was in-hospital mortality, and the secondary outcome measure was cardiac arrest and arrhythmia or QT prolongation on an electrocardiogram.[7]

Results

- Patients in the three treatment groups had more severe disease at baseline than those who received neither drug.
- In adjusted analyses, patients who received one of the three treatment regimens did not show a decreased in-hospital mortality rate when compared with those who received neither drug.
- Patients who received hydroxychloroquine plus azithromycin had a greater risk of cardiac arrest than patients who received neither drug (OR 2.13; 95% CI, 1.12–4.05).

Limitations

Despite the large size of this study, it has the inherent limitations of an observational study. These include residual confounding from confounding variables that were unrecognized and/or unavailable for analysis.

Interpretation

Despite the limitations discussed above, these findings suggest that although hydroxychloroquine and azithromycin are not associated with an increased risk of in-hospital death, the combination of hydroxychloroquine and azithromycin may be associated with an increased risk of cardiac arrest.

Observational Study of Hydroxychloroquine at a Large Medical Center in New York City

This observational study evaluated 1,376 consecutive adults hospitalized with COVID-19. The study assessed the time from study baseline (24 hours after patients arrived at the emergency department) to intubation or death based on whether the patient received hydroxychloroquine at baseline or during follow-up. Patients who received hydroxychloroquine were prescribed a twice-daily dose of hydroxychloroquine 600 mg on the first day followed by 400 mg daily for 4 additional days; this was based on a clinical guidance protocol for the hospital.[8]

Results

- In this study, 811 patients (58.9%) received hydroxychloroquine and 565 (41.1%) did not.
- Hydroxychloroquine recipients were more severely ill at baseline than those who did not receive hydroxychloroquine.
- Using propensity scores to adjust for major predictors of respiratory failure and inverse probability weighting, the study demonstrated that hydroxychloroquine use was not associated with intubation or death (HR 1.04; 95% CI, 0.82–1.32).
- There was also no association between concomitant use of azithromycin and the composite endpoint of intubation or death (HR 1.03; 95% CI, 0.81–1.31).

Limitations

Despite the large size of this study, it has the inherent limitations of an observational study. These include residual confounding from confounding variables that were unrecognized and/or unavailable for analysis.

Interpretation

The use of hydroxychloroquine for treatment of COVID-19 was not associated with harm or benefit in a large observational study.

Observational Cohort of Hydroxychloroquine Versus No Hydroxychloroquine

This retrospective observational cohort study analyzed data for adult patients who were hospitalized for severe COVID-19 pneumonia at four French tertiary care centers. The primary outcome was survival without transfer to the ICU at Day 21. An inverse probability of treatment weighting approach was used to "emulate" randomization.[9]

Results

- Of the 181 patients who were eligible for the analysis, 84 participants received hydroxychloroquine within 48 hours, eight received hydroxychloroquine beyond 48 hours, and 89 did not receive hydroxychloroquine.
- In the hydroxychloroquine group, 18% of the patients received concomitant azithromycin.
- In the inverse probability of treatment-weighted analysis, there was no difference in survival rates without ICU transfer at Day 21 between the hydroxychloroquine group (76% of participants) and the non-hydroxychloroquine group (75% of participants). Similarly, there was no difference between the groups in the secondary outcomes of survival rate and survival rate without acute respiratory distress syndrome at Day 21.

Limitations

This was a retrospective, nonrandomized study.

Interpretation

In this retrospective study, there was no difference in the rates of clinically important outcomes between patients who received hydroxychloroquine within 48 hours of hospital admission and those who did not.

Retrospective Cohort Study that Compared Hydroxychloroquine to No Hydroxychloroquine in a Health Care System in Detroit, Michigan

A comparative, retrospective cohort study assessed the outcomes for all consecutive patients who were hospitalized for COVID-19 (which was defined as a positive SARS-CoV-2 PCR from a nasopharyngeal sample) from March 10 to May 2, 2020, in the Henry Ford Health System in Michigan.[10]

The primary outcome was in-hospital mortality. The study compared outcomes for patients who received hydroxychloroquine alone, hydroxychloroquine plus azithromycin, azithromycin alone, or neither drug.

An interdisciplinary task force of the health system established a COVID-19 treatment protocol that incorporated the use of hydroxychloroquine alone or in combination with azithromycin. The hydroxychloroquine dose was 400 mg twice daily for 1 day, then 200 mg twice daily for 4 days. If azithromycin was used, the dose was azithromycin 500 mg for 1 day, then 250 mg daily for 4 days. The combination of hydroxychloroquine and azithromycin was reserved for patients with severe COVID-19 and minimal cardiac risks. The clinical treatment protocol allowed for the use of tocilizumab and corticosteroids in some patients; however, the criteria for their use were not specified in the report.

Study Population

- The analysis included 2,541 consecutive patients.
- The median patient age was 64 years (IQR 53–76 years); 51% of patients were men, 56% were African American, and 52% had a BMI ≥30.

- The median time to follow-up was 28.5 days (IQR 3–53 days).
- The modified sequential organ failure assessment (mSOFA) score was not available for 25% of patients.
- Corticosteroids were given to 79% of patients in the hydroxychloroquine alone group, 74% of patients in the hydroxychloroquine plus azithromycin group, and 35.7% of those on neither drug.

Mortality

- Overall, crude mortality was 18.1%. When broken down by the different groups, the mortality was 13.5% in hydroxychloroquine alone group, 20.1% in the hydroxychloroquine plus azithromycin group, 22.4% in the azithromycin alone group, and 26.4% in the group that received neither drug ($P < 0.001$).
- Mortality HRs were analyzed using a multivariable Cox regression model; the group that received neither drug was used as the reference. Hydroxychloroquine alone decreased the mortality HR by 66% ($P < 0.001$). Hydroxychloroquine plus azithromycin 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 O_2 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 hydroxychloroquine (95% CI, 0.285–0.832, $P = 0.009$).

Limitations

- This retrospective observational study evaluated one health care system with an institutional protocol for hydroxychloroquine and azithromycin 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 hydroxychloroquine, which suggests that this group may have received less-aggressive care.
- A substantially higher percentage of patients in the hydroxychloroquine arms also received corticosteroids compared to the control arm (77.1% vs. 35.7%). Given that the RECOVERY trial showed that dexamethasone use conferred a survival benefit (see Corticosteroids), it is possible that the findings were confounded by this imbalance in corticosteroid use.[11]

Interpretation

This retrospective, propensity-matched cohort study reported a mortality benefit in hospitalized patients with COVID-19 who received either hydroxychloroquine alone or hydroxychloroquine plus azithromycin compared to receiving neither drug. However, there were substantial imbalances in corticosteroid use between the groups, which may have affected mortality. Moreover, because the study was retrospective and observational, it cannot control for other and unknown confounders.

Other Reviewed Studies

The COVID-19 Treatment Guidelines Panel (the Panel) has reviewed other clinical studies of hydroxychloroquine with or without azithromycin and studies of chloroquine for the treatment of COVID-19.[12-22] These studies have limitations (e.g., the potential for residual confounding, small sample sizes, incomplete reporting, a lack of comparison groups) that make them less definitive and informative than large randomized clinical trials. The Panel's summaries and interpretations of some of those studies are available in the archived versions of the COVID-19 Treatment Guidelines.

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Ivermectin

Last Updated: August 27, 2020

Ivermectin is a Food and Drug Administration (FDA)-approved antiparasitic drug that is used to treat several neglected tropical diseases, including onchocerciasis, helminthiases, 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 has demonstrated an excellent safety profile.[1]

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

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 antiviral response.[3] Ivermectin is therefore a host-directed agent, which is likely the basis for its broad-spectrum activity *in vitro* against the viruses that cause dengue, Zika, HIV, and yellow fever.[3-6]

Recommendation

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

Rationale

Ivermectin has been shown to inhibit the replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in cell cultures.[7] 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.[8,9] 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*.[10,11]

Ivermectin is not approved for the treatment of any viral infection, including SARS-CoV-2 infection. 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.

Clinical Data in Patients With COVID-19

The available clinical data on the use of ivermectin to treat COVID-19 are limited.

Retrospective Analysis of Using Ivermectin in Patients With COVID-19

This study has not been peer reviewed.

This retrospective analysis of consecutive patients with confirmed SARS-CoV-2 infection (27% with severe COVID-19) who were admitted to four Florida hospitals compared patients who received at least one dose of ivermectin (n = 173) to those who received "usual care" (n = 103). The primary outcome was all-cause, in-hospital mortality. The secondary outcomes included mortality in patients with severe disease (defined as "need for either FiO_2 ≥50% or noninvasive or invasive mechanical ventilation") and extubation rates in those who were mechanically ventilated.[12]

Results

- Ivermectin administration was reportedly consistent with hospital guidelines: a single dose of 200 µg/kg, with repeat dosing on Day 7 if the patient was still hospitalized (13 patients received a second dose). Ninety percent of the ivermectin group and 97% of the usual care group received hydroxychloroquine (the majority received hydroxychloroquine in conjunction with azithromycin).

- All-cause mortality was lower among the patients in the ivermectin group than among patients in the usual care group (OR 0.27; $P = 0.03$). The mortality benefit appeared to be limited to the subgroup of patients with severe disease.
- There was no difference between the groups for the median length of hospital stay (7 days in both groups) or the proportion of mechanically ventilated patients who were successfully extubated (36% in the ivermectin group vs. 15% in the usual care group; $P = 0.07$).

Limitations

- This was a retrospective analysis.
- The study included little or no information on oxygen saturation or radiographic findings. It was also unclear whether therapeutic interventions other than hydroxychloroquine, such as remdesivir or dexamethasone, were used in the study.
- The timing of therapeutic interventions was not standardized; if the timing is not accounted for, it can bias the survival comparison.
- The analyses of the durations of ventilation and hospitalization do not appear to account for death as a competing risk.
- No virologic assessments were performed.

Interpretation

The limitations of this retrospective analysis make it difficult to draw conclusions about the efficacy of using ivermectin to treat patients with COVID-19.

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Lopinavir/Ritonavir and Other HIV Protease Inhibitors

Last Updated: July 17, 2020

Lopinavir/ritonavir and darunavir/cobicistat have been studied in patients with COVID-19.

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 is an inhibitor of severe acute respiratory syndrome-associated coronavirus (SARS-CoV) 3CLpro *in vitro*, and this protease appears to be highly conserved in SARS-CoV-2.[2,3] Although lopinavir/ritonavir has *in vitro* activity against SARS-CoV, it is thought to have a poor selectivity index, indicating that higher than tolerable levels of the drug might be required to achieve meaningful inhibition *in vivo*.[4] Lopinavir is excreted in the gastrointestinal tract; therefore, coronavirus-infected enterocytes might be exposed to higher concentrations of the drug.[5]

Darunavir inhibits the 3CLpro enzyme of SARS-CoV-2 and possibly also inhibits the PLpro enzyme. However, in an *in vitro* study, darunavir did not show activity against SARS-CoV-2.[6]

Recommendation

- The COVID-19 Treatment Guidelines Panel **recommends against** using **lopinavir/ritonavir (AI)** or other **HIV protease inhibitors (AIII)** for the treatment of COVID-19, except in a clinical trial.

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. In addition, lopinavir/ritonavir did not show efficacy in a moderately sized randomized controlled trial in patients with COVID-19.

Adverse Effects

The adverse effects 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 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.

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.[7]
- A moderately sized randomized trial failed to find a virologic or clinical benefit of lopinavir/ritonavir over standard of care.[8]
- Results from a small randomized controlled trial showed that darunavir/cobicistat was not effective for the treatment of COVID-19.[9]
- There are no data from clinical trials that support using other HIV protease inhibitors to treat COVID-19.
- Please see Lopinavir/Ritonavir: Selected Clinical Data for more information.

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Lopinavir/Ritonavir: Selected Clinical Data

Last Updated: July 17, 2020

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 for more information on clinical trials that are evaluating lopinavir/ritonavir.

Randomized Controlled Trial of Lopinavir/Ritonavir Versus Standard of Care

In a clinical trial that randomized 199 patients to receive lopinavir 400 mg/ritonavir 100 mg orally twice daily for 14 days or standard of care, patients who were randomized to the lopinavir/ritonavir arm did not have a shorter time to clinical improvement.[1]

Results

- There was a lower, but not statistically significant, mortality rate for the lopinavir/ritonavir group (19.2%) than for the standard of care group (25.0%), and a shorter median intensive care unit stay for those in the lopinavir/ritonavir group than for those in the standard of care group (6 days vs. 11 days; 95% CI, -9 to 0 days).
- There was no difference in the median duration of hospital stay and the median time to clearance of viral RNA from respiratory tract samples between the two arms.
- Nausea, vomiting, and diarrhea were all more frequent among patients in the lopinavir/ritonavir-treated group.

Limitations

- The study was not blinded, which may have affected the assessments of clinical improvement.
- The study was underpowered to show small effects.

Interpretation

A moderately sized, randomized trial failed to find a virologic or clinical benefit of lopinavir/ritonavir over standard of care.

Lopinavir/Ritonavir Plus Interferon Beta-1b Plus Ribavirin in Patients with COVID-19

Also see Interferons for a description of this trial and its results.

An open-label, Phase 2 clinical trial randomized 127 participants with COVID-19 2:1 to receive either a 14-day course of a combination therapy that included interferon beta-1b 8 million international units administered subcutaneously on alternating days (1–3 doses, depending on time from symptom onset) plus lopinavir 400 mg/ritonavir 100 mg orally every 12 hours and ribavirin 400 mg orally every 12 hours, or a 14-day course of lopinavir/ritonavir 400 mg/100 mg every 12 hours alone.[2]

In the combination therapy group, those who were admitted <7 days after symptom onset (n = 52) received triple-drug therapy; however, interferon beta-1b was not included in the regimen for those who were admitted ≥7 days after symptom onset (n = 34) because of concerns regarding its potential for inflammatory effects. The study population consisted of patients who were hospitalized in Hong Kong; the median age was 52 years and the median time from symptom onset to enrollment was 5 days. Only 12% to 14% of participants were on supplemental oxygen, and only one participant was mechanically ventilated.

Results

Patients in the combination therapy group showed faster viral clearance and more rapid clinical improvement than those in the control group.

Limitations

- Participants in both arms received lopinavir/ritonavir, so it is impossible to determine whether lopinavir/ritonavir contributed to the observed treatment effects. However, the possibility that lopinavir/ritonavir may have contributed to the effectiveness of the combination therapy also cannot be ruled out.
- The positive clinical impact of the combination therapy was limited to those who were hospitalized <7 days from symptom onset.
- Most participants in this study had mild illness, and only slightly more than 10% were on supplemental oxygen. For this reason, the study has limited applicability to hospitalized patients in the United States.

Interpretation

This study neither supports nor refutes the use of lopinavir/ritonavir with or without ribavirin in patients with COVID-19. See the Interferons section for further discussion.

Lopinavir/Ritonavir Versus Umifenovir Versus Standard of Care

In a trial of 86 hospitalized patients with mild to moderate COVID-19, 34 patients were randomized to receive lopinavir/ritonavir, 35 patients received the broad-spectrum antiviral umifenovir (trade name Arbidol; not available in the United States), and 17 patients received standard of care.[3]

Results (Comparison of Lopinavir/Ritonavir to Standard of Care)

- The time to a negative severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) nucleic acid pharyngeal swab was similar for patients who received lopinavir/ritonavir (mean duration 9.0 days; SD ± 5.0 days) and for those who received standard of care (mean duration 9.3 days; SD ± 5.2 days).
- Progression to severe illness occurred among six patients (18%) in the lopinavir/ritonavir arm and two patients (12%) who received standard of care.
- Two patients became critically ill; both were randomized to receive lopinavir/ritonavir.

Limitations

- The trial had a small sample size.
- The study was not blinded.
- The effectiveness of umifenovir in treating COVID-19 is unknown.

Interpretation

The small sample size of this trial limits its usefulness.

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.[4]

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 (EC_{50}) for SARS-CoV-2.

Limitations

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

Interpretation

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

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

Last Updated: November 3, 2020

- 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.

Drug Name	Dosing Regimens *The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	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:** • 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.	• Prolonged QTc interval, Torsades de Pointes, AV block, ventricular arrhythmia • Gastrointestinal effects (e.g., nausea, vomiting, diarrhea) • Hepatitis • Hypoglycemia • Hemolysis (especially in patients with G6PD deficiency) • Myopathy • Rash	• 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	• Additive effect with other drugs that prolong the QTc interval (including AZM) or that cause hypoglycemia • CYP2D6 inhibitor (moderate) • P-gp inhibitor	• 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 **(AI)**. • The Panel **recommends against** using high-dose CQ (600 mg twice daily for 10 days) for the treatment of

Drug Name	Dosing Regimens *The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Chloroquine, continued		• 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]			COVID-19 **(AI)**. • Dose-dependent toxicity • A list of clinical trials is available here: Chloroquine
Hydroxychloroquine	**Adults:** • Various loading and maintenance doses have been reported in studies or in clinical care. **Dose Previously Suggested in an EUA for Hospitalized Adults and Adolescents Weighing ≥50 kg:** • 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.	• Prolonged QTc interval, Torsades de Pointes, AV block, ventricular arrhythmia • Gastrointestinal 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]	• 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	• Additive effect with other drugs that prolong the QTc interval (including AZM) or that cause hypoglycemia • CYP2D6 inhibitor (moderate) • P-gp inhibitor	• 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 r**ecommends against** the use of HCQ with or without AZM for the treatment of COVID-19, except in a clinical trial **(AI)**. • Long elimination; half-life is 40–55 days. • Dose-dependent toxicity • A list of clinical trials is available here: Hydroxychloroquine
Lopinavir/Ritonavir	**Adults:** • 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:** • LPV 300 mg/m^2 plus RTV 75 mg/m^2 (maximum dose: LPV 400 mg/RTV 100 mg) PO twice daily for a total of 7 days	• Gastrointestinal effects (e.g., nausea, vomiting, diarrhea) • Transaminase elevation • QTc interval prolongation and Torsades de Pointes have been reported. • PR interval prolongation	• HIV antigen/antibody testing at baseline • Serum transaminase levels • Consider monitoring ECG when LPV/RTV	**High Drug-Drug Interaction Potential** *Lopinavir:* • CYP3A4 inhibitor and substrate *Ritonavir:* • CYP3A4 > CYP2D6 substrate	• The Panel **recommends against** using LPV/RTV **(AI)** or other HIV PIs **(AIII)** to treat COVID-19, except in a clinical trial. • Liquid formulation is commercially available. Crushing LPV/RTV tablets may result in significantly

Drug Name	Dosing Regimens *The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Lopinavir/Ritonavir, continued			is given with other QTc-prolonging medications.	• Potent CYP3A4 and CYP2D6 inhibitor • Inducer of UGT1A1 and CYP1A2, CYP2C8, CYP2C9, and CYP2C19	decreased drug exposure (AUC ↓ 45%).[2] • Use with caution in patients with hepatic impairment. • A list of clinical trials is available here: Lopinavir/Ritonavir
Remdesivir **Note:** RDV is approved by the FDA for the treatment of COVID-19.	**For Hospitalized Adult and Pediatric Patients (Aged ≥12 Years and Weighing ≥40 kg)** *For Patients Who Are Not Mechanically Ventilated and/or on ECMO:* • 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. *For Mechanically Ventilated Patients and/or Patients on ECMO:* • RDV 200 mg IV over 30–120 minutes on Day 1, followed by RDV 100 mg IV on Day 2 through Day 10 **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** *For Patients Weighing 3.5 kg to <40 kg:* • 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	• 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 remdesivir lyophilized powder contains 3 g of SBECD and each 100 mg/20 mL vial of remdesivir solution contains 6 g of SBECD.	• Infusion reactions • Renal function, hepatic function, and prothrombin time should be monitored before and during treatment as clinically indicated • **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.[3]	• Clinical drug-drug interaction studies of RDV have not been conducted. • In vitro, RDV is a substrate of CYP3A4, OATP1B1, and P-gp and an inhibitor of CYP3A4, OATP1B1, OATP1B3, and MATE1.[3] • 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**.[3]	• See Therapeutic Management of Patients with COVID-19 for recommendations on using remdesivir with or without dexamethasone. • RDV should be administered in a hospital or a health care setting that can provide a similar level of care to an inpatient hospital. **Availability:** • 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

Drug Name	Dosing Regimens *The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Remdesivir, continued	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. • For mechanically ventilated patients and/or patients on ECMO, the recommended treatment duration is 10 days. *For Patients Aged <12 Years and Weighing ≥40 kg:* • Same dose as for adults and children aged >12 years and weighing >40 kg			• No significant interaction is expected between RDV and oseltamivir or baloxavir (Gilead Sciences, personal and written communications, August and September 2020).	

[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.[4]

Key: AE = adverse effect; 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; HCQ = hydroxychloroquine; HIV = human immunodeficiency virus; INR = international normalized ratio; IV = intravenous; LPV = lopinavir; LPV/RTV = lopinavir/ritonavir; OATP = organic anion transporter polypeptide; the Panel = the COVID-19 Treatment Guidelines Panel; P-gp = P-glycoprotein; PI = protease inhibitor; PMA = postmenstrual age; PO = orally; PT = prothrombin time; 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

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Immune-Based Therapy Under Evaluation for Treatment of COVID-19

Last Updated: July 17, 2020

Given the hyperactive inflammatory effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), agents that modulate the immune response are being explored as adjunctive treatments for the management of moderate to critical COVID-19.[1] These agents include human blood-derived products and immunomodulatory therapies.

Some human blood-derived products are obtained from individuals who have recovered from SARS-CoV-2 infection (e.g., convalescent plasma, immunoglobulin products).[2,3] These heterogenous products are postulated to have either direct antiviral properties, such as with convalescent plasma, and/or immunomodulatory effects like those noted with mesenchymal stem cells.[4] Additionally, neutralizing monoclonal antibodies directed against SARS-CoV-2 have been developed and are under investigation in clinical trials.[5]

Other agents in this group include therapeutics currently approved for the treatment of other immune and/or inflammatory syndromes. These agents include corticosteroids (e.g., glucocorticoids),[6] which as a class possess a broad array of mechanisms to abrogate systemic inflammation, and more targeted anti-inflammatory treatments such as interleukin inhibitors,[7,8] interferons,[9] kinase inhibitors,[10] and others.

In the following sections of the COVID-19 Treatment Guidelines, different blood-derived products and immunomodulators under investigation for the management of COVID-19 are discussed. Items discussed include the proposed rationale for use of these therapies, the clinical safety and efficacy data to date, and the COVID-19 Treatment Guidelines Panel's recommendations for their use.

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Blood-Derived Products Under Evaluation for the Treatment of COVID-19

Last Updated: July 17, 2020

Summary Recommendations
• There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of the following blood-derived products for the treatment of COVID-19: • **COVID-19 convalescent plasma** • **Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunoglobulins** • The Panel **recommends against** the use of the following blood-derived products for the treatment of COVID-19, except in a clinical trial: • **Mesenchymal stem cells (AII)** • **Non-SARS-CoV-2-specific intravenous immunoglobulins (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.
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

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 ≥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 [PaO_2/FiO_2] <200 mmHg or shock) were excluded. The primary outcome was time to disease progression through 28 days (i.e., to PaO_2/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 ≥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.

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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.

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-IVG 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.

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Mesenchymal Stem Cells

Last Updated: October 9, 2020

Mesenchymal stem cells are investigational products that have been studied extensively for broad clinical applications in regenerative medicine[1] 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 **(AII)**.

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 potentially 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 programs, 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, mesenchymal stem cells lack the angiotensin-converting enzyme 2 receptor that SARS-CoV-2 uses for viral entry into cells; therefore, mesenchymal stem cells are resistant to infection.[5,6]

Clinical Data

Data supporting the use of mesenchymal stem cells in patients with 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 control patients, one died, one developed acute respiratory distress syndrome (ARDS), and one remained stable with severe disease.[7]

- A small clinical trial evaluated human umbilical cord mesenchymal stem cell (hUC-MSC) infusion in patients with severe COVID-19 who had not responded to standard of care therapies after 7 to 10 days of treatment. The standard of care therapies included supplemental oxygen, umifenovir/oseltamivir, antibiotics if indicated, and glucocorticosteroids. The study was intended as a randomized controlled trial; however, due to the lack of sufficient hUC-MSCs, it was not possible to randomize the participants as originally planned. Among the 41 patients eligible to participate in the study, 12 received hUC-MSC infusion and 29 received standard of care therapies only. The study arms were well balanced with regard to demographic characteristics, laboratory test results, and disease severity. All 12 participants who received hUC-MSC infusion recovered without requiring mechanical ventilation and were discharged to home, whereas four patients who received only standard of care therapies progressed to critical illness requiring mechanical ventilation, and three of these patients died. These results are not statistically significant and interpretation of the study is limited by its 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. In the mesenchymal stem cell group, three patients (17.6%) died; in the control group, 24 patients (54.5%) died. 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* for a list of clinical trials evaluating mesenchymal stem cells for the treatment of COVID-19, COVID-19-related ARDS, and COVID-19-associated multiorgan system 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 on the efficacy and safety of mesenchymal stem cell use in children.

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Immunomodulators Under Evaluation for the Treatment of COVID-19

Last Updated: November 3, 2020

Summary Recommendations
Dexamethasone and Other Corticosteroids • The COVID-19 Treatment Guidelines Panel's (the Panel's) recommendations on the use of dexamethasone (or other corticosteroids) with or without remdesivir can be found in the Therapeutic Management of Patients with COVID-19. **Other Immunomodulators** 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: • Interleukin (IL)-1 inhibitors (e.g., **anakinra**). • **Interferon beta** for the treatment of early (i.e., <7 days from symptom onset) mild and moderate COVID-19. The Panel **recommends against** the use of the following immunomodulators for the treatment of COVID-19, except in a clinical trial: • Anti-IL-6 receptor monoclonal antibodies (e.g., **sarilumab**, **tocilizumab**) or anti-IL-6 monoclonal antibody (**siltuximab**) **(BI)**. • **Interferons (alfa or beta)** for the treatment of severely or critically ill patients with COVID-19 **(AIII)**. • Bruton's tyrosine kinase inhibitors (e.g., **acalabrutinib**, **ibrutinib**, **zanubrutinib**) and Janus kinase inhibitors (e.g., **baricitinib**, **ruxolitinib**, **tofacitinib**) **(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

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 Clinical Data to Date, below.[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 Clinical Data to Date, below.[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.

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 HBV[25] 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* for the latest information.

Clinical Data to Date

Multicenter Randomized Controlled Trial of Dexamethasone Versus Standard of Care in Hospitalized Patients

Study Design

The RECOVERY study is an ongoing, multicenter, open-label, adaptive trial sponsored by the National Health Service in the United Kingdom. Eligible participants were randomized to receive one of several potential treatments for COVID-19 plus the standard of care or the standard of care alone. In one study arm, dexamethasone 6 mg daily was administered either orally or intravenously for up to 10 days or until hospital discharge, whichever came first. The primary study endpoint was all-cause mortality at 28 days after randomization. Secondary endpoints included time to hospital discharge, cause-specific mortality, need for renal replacement, major cardiac arrhythmia, and receipt and duration of ventilation. The results for the dexamethasone plus the standard of care versus the standard of care alone comparison are described below.[1]

Study Population

Hospitalized patients with clinically suspected or laboratory-confirmed SARS-CoV-2 infection were eligible for enrollment. Patients were not enrolled into the dexamethasone study arm (or included in the analysis) if their physicians determined that the risks of participation were too great based on their medical history or that corticosteroid therapy was indicated outside the study.

Preliminary Results

Participant characteristics

- The preliminary analysis included 6,425 participants: 2,104 participants in the dexamethasone plus standard of care arm and 4,321 in the standard of care alone arm.
- SARS-CoV-2 infection was confirmed by laboratory testing in 89% of the participants.
- The mean age of the participants was 66 years, 64% were men, 56% had at least one major

comorbidity, and 24% had diabetes.

- At randomization, 16% of the participants received invasive mechanical ventilation or extracorporeal membrane oxygenation, 60% required supplemental oxygen but not invasive ventilation, and 24% required no oxygen supplementation.
- Few participants received remdesivir, hydroxychloroquine, lopinavir/ritonavir, or tocilizumab (0% to 3% of the participants in both arms); approximately 8% of the participants in the standard of care alone arm received dexamethasone after randomization.

Study endpoint analyses

- Overall, 22.9% of participants in the dexamethasone arm and 25.7% in the standard of care arm died within 28 days of study randomization (age-adjusted rate ratio 0.83; 95% CI, 0.75–0.93; $P < 0.001$).
- There was an interaction between baseline severity of COVID-19 and the treatment effect of dexamethasone.
  - Survival benefit appeared greatest among participants who required invasive mechanical ventilation at randomization: 29.3% of participants in the dexamethasone arm died within 28 days versus 41.4% in the standard of care arm (rate ratio 0.64; 95% CI, 0.51–0.81).
  - Among patients who required supplemental oxygen but not mechanical ventilation at enrollment, 23.3% of participants in the dexamethasone arm and 26.2% in the standard of care arm died within 28 days (rate ratio 0.82; 95% CI, 0.72–0.94).
  - No survival benefit was seen among participants who did not require oxygen therapy at enrollment; 17.8% of participants in the dexamethasone arm and 14.0% in the standard of care arm died within 28 days (rate ratio 1.19; 95% CI, 0.91–1.55).
- The risk of progression to invasive mechanical ventilation was lower in the dexamethasone arm than in the standard of care arm (rate ratio 0.77; 95% CI, 0.62–0.95).

Limitations

- The study was randomized, but open label.
- In this preliminary report, the results for key secondary endpoints (e.g., cause-specific mortality, need for renal replacement), potential adverse events, and efficacy of dexamethasone in key subgroups (e.g., patients with comorbidities) have not been reported.
- 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 this group was ventilated.
  - It is unclear if 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. If so, then the disease severity would vary by age within the oxygen group, contributing to the difficulty in interpreting the observed mortality benefit in this heterogeneous group.
- Very few pediatric or pregnant patients with COVID-19 were included in the RECOVERY trial; therefore, the safety and efficacy of dexamethasone for the treatment of COVID-19 in children or

in pregnant individuals are unknown.

Interpretation

In patients with severe COVID-19 who required oxygen support, using dexamethasone 6 mg daily for up to 10 days reduced mortality at 28 days. The benefit of dexamethasone was most apparent in hospitalized patients who were mechanically ventilated. There was no observed benefit of dexamethasone in patients who did not require oxygen support.

Meta-Analysis of Corticosteroids for Critically Ill Patients With COVID-19

Study Design

This meta-analysis performed by the World Health Organization (WHO) included pooled data from seven randomized clinical trials of corticosteroids in critically ill patients with COVID-19.[20]

Patient Population

- The analysis included 1,703 critically ill patients with COVID-19 who were participants in trials conducted in 12 countries from February 26 to June 9, 2020.
- Across the studies, 678 patients received corticosteroids (i.e., dexamethasone, hydrocortisone, methylprednisolone), and 1,025 received usual care or placebo.
- Overall, 1,559 of the patients (91.5%) were on mechanical ventilation.
- The median age of the patients was 60 years (IQR 52–68 years); 488 (28.7%) were women.
- Across the six trials that provided data on the use of vasoactive agents, 47.0% of the patients were on the agents at randomization.
- Mortality was assessed at 28 days (five trials), 21 days (one trial), and 30 days (one trial).

Results

Key primary and secondary outcomes

- The reported mortality was 32.7% (222 of 678 patients) in the corticosteroids group and 41.5% (425 of 1,025 patients) in the usual care or placebo group (summary OR 0.66 [95% CI, 0.53-0.82; $P < 0.001$] based on a fixed-effect meta-analysis).
- The fixed-effect summary ORs for the association with all-cause mortality were:
  - Dexamethasone: OR 0.64 (95% CI, 0.50–0.82; $P < 0.001$) in three trials with 1,282 patients
  - Hydrocortisone: OR 0.69 (95% CI, 0.43–1.12; $P = 0.13$) in three trials with 374 patients
  - Methylprednisolone: OR 0.91 (95% CI, 0.29–2.87; $P = 0.87$) in one trial with 47 patients
  - For patients on mechanical ventilation (n = 1,559): OR 0.69 (95% CI, 0.55–0.86) corresponding to an absolute risk of 30% for corticosteroids versus 38% for usual care or placebo
  - For patients not on mechanical ventilation (n = 144): OR 0.41 (95% CI, 0.19–0.88) corresponding to an absolute risk of 23% for corticosteroids versus 42% for usual care or placebo
  - For the association between corticosteroids and mortality among patients who were receiving vasoactive agents at randomization: OR 1.05 (95% CI, 0.65–1.69) (an absolute risk of 48% for corticosteroids vs. 47% for usual care or placebo)
  - For the association between corticosteroids and mortality among patients who were not receiving vasoactive agents at randomization: OR 0.55 (95% CI, 0.34–0.88) (an absolute risk of 24% for corticosteroids vs. 37% for usual care or placebo)

Safety

- Serious adverse events were reported in six of the seven trials. Serious adverse events occurred in 18.1% of the patients randomized to corticosteroids (64 of 354 patients) and in 23.4% of the patients randomized to usual care or placebo (80 of 342 patients).

Limitations

- The design of the trials included in the meta-analysis differed in several ways, including the following:
  - Definition of critical illness, which ranged from requirement for oxygen supplementation >10 L/minute to requirement for intubation with moderate to severe acute ARDS
  - Specific corticosteroid used
  - Dose of corticosteroid: high dose in three trials (322 patients), low dose in four trials (1,381 patients)
  - Control group: usual care in five trials, placebo in two trials
  - Duration of corticosteroid treatment
  - Reporting of serious adverse events
- The RECOVERY trial accounted for 59.1% of the participants (1,007) in this meta-analysis, and participants from the other six trials accounted for 40.9% of the total population (696 participants). Three trials enrolled fewer than 50 patients.
- Some of the trials closed early after the results from the RECOVERY trial were reported.
- Some studies required that participants had confirmed SARS-CoV-2 infection; others enrolled participants with either probable or confirmed infection. Confirmed cases ranged from 79% to 100% across the trials.
- Although the risk of bias was low in six of the seven trials, it was assessed as "some concerns" for one trial. This trial contributed only 47 patients to the analysis.

Interpretation

Systemic corticosteroids decrease 28-day mortality in patients with COVID-19 without safety concerns, based on the meta-analysis of the seven randomized controlled trials. Because most of the participants (59%) in this meta-analysis were from the RECOVERY trial, it is likely that the benefits observed were mostly associated with dexamethasone, the corticosteroid used in the RECOVERY trial.

Single-Center Randomized Controlled Trial of Methylprednisolone Versus Placebo in Hospitalized Patients in Brazil

Study Design

Methylprednisolone as Adjunctive Therapy for Patients Hospitalized With COVID-19 (Metcovid) is a randomized, double-blind, placebo-controlled, single-center study in Brazil that evaluated the use of short-course methylprednisolone (0.5 mg/kg twice daily for 5 days) versus placebo in hospitalized patients with confirmed or suspected COVID-19 pneumonia.[16]

Results

Participant characteristics

- A total of 416 participants were randomized; 393 were included in the modified intention-to-treat (mITT) analysis (194 from the methylprednisolone arm and 199 from the placebo arm).
- SARS-CoV-2 infection was confirmed in 83% and 79% of the participants who received

methylprednisolone and placebo, respectively.

- The mean age of the participants was 55 years; 65% were men and 29% had diabetes.
- At enrollment, 34% of the participants in each group required invasive mechanical ventilation, and 51% of the participants in the methylprednisolone group and 45% in the placebo group required supplemental oxygen.
- The median time from illness onset to randomization was 13 days (IQR 9–16) in both groups.
- Among the participants who required mechanical ventilation at study entry, the median time from mechanical ventilation to randomization was 4 days in the methylprednisolone arm and 3 days in the placebo arm.
- None of the participants received anti-interleukin (IL)-6, anti-IL-1, remdesivir, or convalescent plasma.
- Hydrocortisone use (per clinician discretion) in patients with shock was reported in 8.7% and 7.0% of the participants in the methylprednisolone and placebo groups, respectively.

Study endpoints

- *Primary outcome:* There was no difference between the arms in 28-day mortality: 37.1% of the participants in the methylprednisolone arm and 38.2% in the placebo arm died by Day 28 (HR 0.92; 95% CI, 0.67–1.28; *P* = 0.629).
- *Secondary outcomes:* There was no difference between the arms in early mortality at Days 7 and 14 or in the need for mechanical ventilation by Day 7.
  - Mortality at Day 7: 16.5% and 23.6% of participants in the methylprednisolone and placebo arms, respectively (HR 0.68; 95% CI, 0.43–1.06; *P* = 0.089)
  - Mortality at Day 14: 27.3% and 31.7% of participants in the methylprednisolone and placebo arms, respectively (HR 0.82; 95% CI, 0.57–1.18; *P* = 0.29)
  - Need for mechanical ventilation by Day 7: 19.4% and 16.8% of participants in the methylprednisolone and placebo arms, respectively (*P* = 0.65)
- *Post-hoc analysis:* The 28-day mortality rate in participants aged >60 years was lower in the methylprednisolone group than in the placebo group (46.6% vs. 61.9% of participants, respectively; HR 0.63; 95% CI, 0.41–0.98; *P* = 0.039).
- There was no difference between the groups in the proportion of patients who were reverse transcription polymerase chain reaction (RT-PCR) positive at Day 7 (52.1% in the methylprednisolone arm and 52.6% in the placebo arm).

Safety

- Differences in the need for insulin therapy between the methylprednisolone and placebo groups were not significant (59.5% vs. 49.4% of patients, respectively; *P* = 0.059), nor were rates of positive blood cultures at Day 7 (8.3% vs. 8.0%, respectively), or sepsis until Day 28 (38.1% vs. 38.7% of patients, respectively).

Limitations

- This is a single-center study with a moderate sample size.
- 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.

Interpretation

The use of methylprednisolone 0.5 mg/kg twice daily for up to 5 days did not reduce 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. This study used weight-based dosing of methylprednisolone, which was approximately double the equivalent dose of dexamethasone used in the RECOVERY trial. The treatment duration was shorter (i.e., 5 days of methylprednisolone therapy vs. 10 days of dexamethasone therapy in the RECOVERY trial). Methylprednisolone is an intermediate acting corticosteroid with a shorter half-life than dexamethasone. Lastly, the median time from symptom onset to receipt of corticosteroids in this study was approximately 5 days longer than in the RECOVERY trial.

Multicenter Randomized Controlled Trial of Dexamethasone Versus Standard of Care in Patients Admitted to Intensive Care Units in Brazil

Study Design

This multicenter, randomized, open-label clinical trial conducted in 41 intensive care units (ICUs) in Brazil evaluated the use of intravenous dexamethasone (20 mg daily for 5 days, then 10 mg daily for 5 days or until ICU discharge) plus standard of care versus the standard of care alone in patients with COVID-19 and moderate to severe ARDS.[17]

Study Population

This study enrolled ICU patients who were receiving mechanical ventilation within 48 hours of meeting the criteria for moderate to severe ARDS (a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen [PaO_2:FiO_2] ≤ 200 mmHg).

Results

- A total of 299 patients were randomized to dexamethasone (n = 151) or the standard of care (n = 148).
- The dexamethasone group included more women than the standard of care group (40.4% vs. 34.5%), more patients with obesity (30.5% vs. 23.7%), and fewer patients with diabetes (37.8% vs. 46.6%).
- Baseline characteristics were similar for the dexamethasone and standard of care groups: mean age of 60 years versus 63 years, vasopressor use by 66% versus 68% of patients, and mean PaO_2:FiO_2 of 131 mmHg versus 133 mm Hg.
- The median time from symptom onset to randomization for both groups was 9 to 10 days; the median time from mechanical ventilation to randomization was 1 day.
- None of the patients received remdesivir; anti-IL-6 and convalescent plasma were not widely available.
- The median duration of dexamethasone therapy was 10 days (IQR 6–10 days).
- Of note, 35.1% of the patients in the standard of care group also received corticosteroids.

Study endpoints

- *Primary outcome:* The mean number of days alive and free from mechanical ventilation by Day 28 was higher in the dexamethasone group than in the standard of care group (6.6 days vs. 4.0 days, respectively, estimated difference of 2.3 days; 95% CI, 0.2–4.4; *P* = 0.04).
- *Secondary outcomes:* There was no difference between the groups for the following parameters:
    - All-cause mortality at Day 28 (56.3% in the dexamethasone group vs. 61.5% in the standard of care group: HR 0.97; 95% CI, 0.72–1.31; *P* = 0.85)

    - ICU-free days during the 28 days (dexamethasone group: mean of 2.1 days; 95% CI, 1.0–4.5 days vs. standard of care: mean of 2.0 days; 95% CI, 0.8–4.2 days; *P* = 0.50)
    - Duration of mechanical ventilation during the 28 days (dexamethasone group: mean of 12.5 days; 95% CI, 11.2–13.8 days vs. standard care group: mean of 13.9 days; 95% CI, 12.7–15.1 days; *P* = 0.11)
    - Score on 6-point WHO ordinal scale at Day 15 (median score of 5 for both groups, dexamethasone group: IQR 3–6; standard of care group: IQR 5–6; OR 0.66: 95% CI, 0.39–1.13; *P* = 0.07)
- The mean sequential organ failure assessment (SOFA) score at 7 days was lower in the dexamethasone group (6.1; 95% CI, 5.5–6.7) than in the standard of care group (7.5; 95% CI, 6.9–8.1) (difference -1.16; 95% CI, -1.94 to -0.38; *P* = 0.004).
- *Post-hoc analyses*
    - The dexamethasone group had a lower cumulative probability of death or mechanical ventilation at Day 15 than the standard of care group (67.5% vs. 80.4%, respectively; OR 0.46; 95% CI, 0.26–0.81; *P* = 0.01).
    - The proportion of patients discharged alive within 28 days was 27.8% in the dexamethasone group versus 16.9% in the standard of care group (*P* = 0.07).

Safety

- Safety was comparable for the dexamethasone and standard of care groups: need for insulin, 31.1% versus 28.4%; new infections, 21.9% versus 29.1%; bacteremia, 7.9% versus 9.5%; other serious adverse events, 3.3% versus 6.1%.

Limitations

- This is an 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 standard of care 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.

Interpretation

Compared with the standard of care alone, dexamethasone at a higher dose than used in the RECOVERY trial plus standard care 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. Dexamethasone was not associated with an increased risk of adverse events in this population. More than one-third of those randomized to the standard care alone group also received corticosteroids; however, it is impossible to determine the effect of corticosteroid use in these patients on the overall study outcomes.

Multicenter Randomized Controlled Trial of Hydrocortisone Versus Placebo in Patients Admitted to ICUs in France

Study Design

Community-Acquired Pneumonia: Evaluation of Corticosteroids in Coronavirus Disease (CAPE COVID) is a multicenter, randomized, double-blind, sequential trial conducted in nine French ICUs that evaluated hydrocortisone versus placebo (1:1 randomization) in patients with confirmed or suspected COVID-19 and acute respiratory failure.[18]

- The treatment regimen was continuous infusion hydrocortisone 200 mg/day until Day 7, then decreased to hydrocortisone 100 mg/day for 4 days, and then to 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.
- The trial was embedded in a parent trial (Community-Acquired Pneumonia: Evaluation of Corticosteroids [CAPE COD]) designed to evaluate hydrocortisone therapy in severely ill ICU patients with community-acquired pneumonia.
- The planned sample size was 290 participants, but only 149 patients were enrolled because the study was terminated early following release of the results from the RECOVERY trial.

Study Population

Patients enrolled in the study had confirmed or radiographically suspected COVID-19, with at least one of four severity criteria:

- Need for mechanical ventilation with a positive end-expiratory pressure (PEEP) ≥5 cmH_20
- High-flow oxygen with a PaO_2:FiO_2 ratio <300 mmHg and with an FiO_2 value ≥50%
- Reservoir mask oxygen with a PaO_2:FiO_2 ratio <300 mmHg (estimated)
- Pneumonia severity index >130 (scoring table)

Results

- The study enrolled 149 participants; 76 were randomized to hydrocortisone and 73 to placebo, 148 completed the study, and 149 were included in the primary (ITT) analysis.
- There was no obvious difference between the groups in baseline participant characteristics (reported by group, not overall):
  - The mean participant age was 62.2 years, 70% of the participants were men, and the median participant body mass index (BMI) was approximately 28.
  - SARS-CoV-2 infection was confirmed in 96% of the participants overall.
  - The median symptom duration before randomization was approximately 9 days in the hydrocortisone group and 10 days in the placebo group.
  - Approximately 18% of the participants had diabetes, 7% had chronic obstructive pulmonary disease or asthma, and 6% were immunosuppressed.
  - Participant baseline laboratory values were similar, including serum cortisol levels.
  - At baseline, 81% of the patients were mechanically ventilated.
  - The median systolic blood pressure was numerically higher in the placebo group than in the hydrocortisone group (127 mmHg vs. 112 mmHg).
    - At baseline, vasopressors were administered in 24% of the hydrocortisone-treated patients and 18% of the placebo-treated patients.

- There was no difference between the groups in the use of concomitant therapies for COVID-19 at baseline (approximately 3% of participants used remdesivir, 14% used lopinavir/ritonavir, 13% used hydroxychloroquine, and 34% used hydroxychloroquine plus azithromycin).
- The median duration of treatment was 10.5 days for hydrocortisone-treated patients versus 12.8 days for the placebo-treated patients ($P = 0.25$).

Study Endpoints

- *Primary outcome:* Treatment failure (defined as death or persistent dependency on mechanical ventilation or high-flow oxygen) on Day 21 occurred in 32 of 76 patients (42.1%) in the hydrocortisone group and in 37 of 73 patients (50.7%) in the placebo group (difference of proportions -8.6%; 95% CI, -24.9% to 7.7%; $P = 0.29$).
- *Secondary outcomes:* There were no differences between the groups in the need for intubation, rescue strategies, or oxygenation (i.e., change in PaO_2:FiO_2 ratio).
  - Among the patients who did not require mechanical ventilation at baseline, 8 of 16 patients (50%) in the hydrocortisone group required subsequent intubation versus 12 of 16 patients (75%) in the placebo group.
- *Post-hoc analyses*
  - Clinical status on Day 21 did not significantly differ between the groups (although there were fewer deaths in the hydrocortisone group than in the placebo group [14.7% vs. 27.4%; $P = 0.06$]).
  - By Day 21, 57.3% of the hydrocortisone-treated patients were discharged from the ICU versus 43.8% of the placebo-treated patients.
  - By Day 21, 22.7% of the hydrocortisone-treated patients versus 23.3% of the placebo-treated patients were still mechanically ventilated.

Safety

- Apart from deaths, three serious adverse events were reported (cerebral vasculitis, cardiac arrest due to pulmonary embolism [PE], and intra-abdominal hemorrhage from anticoagulation for PE). All occurred in the hydrocortisone group; however, none were attributed to the intervention. There was no difference between the hydrocortisone and placebo groups in nosocomial infections.

Limitations

- The sample size was small.
- The study collected limited information about comorbidities (e.g., hypertension).
- The race and/or ethnicity of the study participants was not reported.
- Nosocomial infections were recorded but not adjudicated.

Interpretation

Compared to placebo, hydrocortisone does 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 doses of hydrocortisone used in the CAPE COVID 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.

Multicenter International Randomized Controlled Trial Performed on an Adaptive Platform

Study Design

The Randomised, Embedded, Multifactorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) study used an adaptive platform trial testing multiple interventions in a pragmatic, randomized controlled trial.[19]

Key elements of the study design

- Randomized platform trial across 121 sites in eight countries
- Open-label comparison of multiple treatment arms within multiple therapeutic domains
- Primary analysis:
  - Includes patients with severe COVID-19
  - Bayesian cumulative logistic model adjusted for age, sex, site, region, time, assignment to interventions within other domains, and domain and intervention eligibility

Key primary outcome

- Days free of respiratory and cardiovascular organ support up to Day 21
  - The outcome assigned to patients who died was -1 day.

Key secondary outcomes

- In-hospital mortality
- Need for mechanical ventilation
- Composite of progression to mechanical ventilation, extracorporeal membrane oxygenation, or death

Patient Population

- A total of 403 patients with severe COVID-19 were randomized to open-label hydrocortisone within 36 hours of ICU admission.
- Three arms were included within the corticosteroid domain:
  - Hydrocortisone 50 mg four times daily for 7 days (n = 143)
  - Septic shock-based hydrocortisone dosing (hydrocortisone 50 mg four times daily for the duration of shock; n = 152). Note that five patients in this group with unknown outcomes were removed from study analysis.
  - No hydrocortisone (n = 108)

Results

- Patient demographics for enrolled patients in the corticosteroid arms:
  - The mean age was 59.5 to 60.4 years.
  - 70.6% to 71.5% were men.
  - The mean BMI was between 29.7 and 30.9.
  - 50% to 63.5% received mechanical ventilation.
- Enrollment was halted after announcement of the RECOVERY trial results.
- There was no significant difference in mortality across the groups:
  - The median adjusted OR was 1.43 (95% credible interval, 0.91–2.27) for the fixed-duration

hydrocortisone group compared to the no hydrocortisone group.
    - The median adjusted OR was 1.22 (95% credible interval, 0.76–1.94) for the shock-dependent hydrocortisone group compared to the no hydrocortisone group.
    - The model-based primary analysis included all the study arms. The analysis was repeated including only those eligible for corticosteroids, and the results were fundamentally unchanged.

Limitations

- The study was terminated early because of release of the RECOVERY study results.
- The study was randomized, but open label.

Interpretation

Corticosteroids did not significantly increase support-free days in either the fixed-dose hydrocortisone or shock-dependent hydrocortisone group, although the early termination of the trial led to limited power to detect difference between the study arms.

Retrospective Cohort Study That Compared Corticosteroids to No Corticosteroids in a Single Hospital in Shanghai, China

Study Design

This was a retrospective cohort study in patients with nonsevere COVID-19 pneumonia and propensity score-matched controls.[28]

Study Population

- This study enrolled 475 patients with nonsevere COVID-19 pneumonia on a chest computerized tomography (CT) scan who were hospitalized at the Shanghai Public Health Clinical Center from January to June 2020. Among these patients, 55 had received early, low-dose corticosteroid therapy (50 received intravenous methylprednisolone 20 mg/day or 40 mg/day for 3 to 5 days, and five received prednisone 20 mg/day [the methylprednisolone-equivalent dose] for 3 days), and 420 did not receive any corticosteroids. Using propensity scores, 55 of the 420 patients were selected as matched controls. Study results refer to these 55 case-control pairs.
- Patients with severe pneumonia were excluded from the study. Severe pneumonia was defined as having any of the following: respiratory distress, respiratory rates >30/minute, pulse oxygen saturation <93%, oxygenation index <300 mmHg, mechanical ventilation, or shock. Patients who required immediate ICU admission at hospitalization or who used corticosteroids after progression to severe disease were also excluded from the study.

Results

- Baseline characteristics: The corticosteroid and control groups were well-matched with respect to the measured covariates. Patients in both groups had a median age of 58 to 59 years and a median oxygen saturation of 95%; 42% of the participants in the corticosteroid group and 46% in the control group had comorbidities, including 35% to 36% with hypertension and 11% to 13% with diabetes.
- Corticosteroids were administered at a median of 2 days (IQR 1–5 days) after hospital admission.
- *Primary outcomes*
    - Seven patients (12.7%) in the corticosteroid group developed severe disease, compared with one patient (1.8%) in the control group ($P = 0.028$); HR 2.2 (95% CI, 2.0 to 2.3; $P < 0.001$ for time to severe disease).
    - There was one death in the methylprednisolone group and none in the control group.

- *Secondary outcomes:* Duration of fever (5 days vs. 3 days), virus clearance time (18 days vs. 11 days), and length of hospital stay (23 days vs. 15 days) were all longer in the corticosteroid group ($P < 0.001$ for each outcome). More patients in the corticosteroid group than in the control group were prescribed antibiotics (89% vs. 24% of patients, respectively) and antifungal therapy (7% vs. 0% of patients, respectively).

Limitations

- This was a retrospective, case-control study.
- The sample size was small (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 adjust for some of the unmeasured confounders.
- It is unclear if the results of this study would apply to corticosteroids other than methylprednisolone.
- Patients who used corticosteroids after progression to severe disease were excluded from the retrospective study. This exclusion requirement could introduce selection bias in favor of the control group.

Interpretation

In this study, methylprednisolone therapy in patients with nonsevere COVID-19 pneumonia was associated with worse outcomes. However, this finding is difficult to interpret because of the potential confounding factors in this nonrandomized, case-control study. It is unclear if the results for methylprednisolone therapy can be generalized to therapy with other corticosteroids.

Other Clinical Studies of Corticosteroid Use in COVID-19

Other smaller, retrospective cohort, and case-series studies have yielded conflicting results on the efficacy of corticosteroids for the treatment of COVID-19.[29-36] Several studies demonstrated the clinical benefit of using low-dose methylprednisolone early in the course of infection; the benefits included more rapid resolution of hypoxia, less need for mechanical ventilation, fewer ICU transfers, and shorter hospital stays. Additionally, other studies suggest a benefit of corticosteroids in lowering overall mortality in patients with moderate disease, severe disease, and ARDS, which is consistent with results from the RECOVERY study.

Conversely, results reported for other studies, including a meta-analysis of 15 studies in patients with coronavirus infections (e.g., COVID-19, SARS, MERS)[37] and a retrospective review of critically ill patients with COVID-19, suggest an increased risk of multiorgan dysfunction and no mortality benefit (and potentially an increased risk of death) with use of corticosteroids.[38] These study results should be interpreted with caution, as the studies are retrospective and have methodological problems.

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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 MERS[6] 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 syndrome[10] 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* 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.

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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 (SpO_2 ≤93% with ≥6L/min O_2) or worsening hypoxia (SpO_2 ≤93% with >3L/min O_2 and a loss of ≥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 kg/m^2 vs. 29.0 kg/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 ≥100 mg/L and/or ferritin ≥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* 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.

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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). 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*.

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* Identifier 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 PaO_2/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 PaO_2/FiO_2 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://www.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 therapy[9] 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.

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Kinase Inhibitors: Bruton's Tyrosine Kinase Inhibitors and Janus Kinase Inhibitors

Last Updated: July 17, 2020

Recommendation

The COVID-19 Treatment Guidelines Panel **recommends against** the use of **Bruton's tyrosine kinase (BTK) inhibitors**, such as **acalabrutinib**, **ibrutinib**, and **zanubrutinib**; and **Janus kinase (JAK) inhibitors**, such as **ruxolitinib** and **tofacitinib**; for the treatment of COVID-19, except in a clinical trial **(AIII)**.

For recommendations on using **baricitinib** under the Emergency Use Authorization issued by the Food and Drug Administration (FDA), please refer to this statement. The Panel plans to update the information on using baricitinib in this section soon.

Rationale

BTK inhibitors and JAK inhibitors have broad immunosuppressive effects. Ongoing clinical trials should help clarify their role in the treatment of COVID-19.

BTK inhibitors are licensed by the FDA for the treatment of B-cell malignancies.[1] BTK is a signaling molecule of the B-cell antigen receptor and cytokine receptor pathways. BTK's role in signaling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis, and adhesion.[2]

JAK inhibitors are potent immunosuppressive agents that are FDA approved for the treatment of rheumatoid arthritis, psoriatic arthritis, polycythemia vera, myelofibrosis, ulcerative colitis, and graft-versus-host disease. JAK inhibitors interfere with phosphorylation of signal transducer and activator of transcription (STAT) proteins[3,4] that are involved in vital cellular functions, including signaling, growth, and survival. Phosphorylation of STAT proteins involved in these pathways can increase or decrease their function, and aberrant activation of these proteins has been associated with autoimmune disorders and cancers.[5] JAKs transmit cytokine signaling by pairing with another JAK (e.g., JAK1/JAK2, JAK1/JAK3); however, whether inhibition of specific JAKs is relevant to therapeutic effectiveness is unknown.

Rationale for Use in Patients With COVID-19

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).[6] This immunosuppression could potentially reduce the inflammation and associated immunopathologies that have been 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.[7]

Adverse Effects

Most of the data on adverse effects of BTK and 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. Hemorrhage and cardiac arrhythmia have occurred in patients who received BTK inhibitors. Thrombotic events and gastrointestinal perforation have occurred in patients who received JAK inhibitors.

Considerations in Pregnancy

- BTK inhibitors: There is a paucity of data on human pregnancy and BTK inhibitor use. In animal studies, in doses exceeding the therapeutic human dose, acalabrutinib and ibrutinib were associated with interference with embryofetal development.[8,9] Based on these data, BTK inhibitors may be associated with fetal malformations when use occurs during organogenesis. The impact of use later in pregnancy is unknown. Risks of use should be balanced against potential benefits.
- JAK inhibitors: There is a paucity of data on the use of JAK inhibitors in pregnancy. Fetal risk cannot be ruled out. 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.[10-12] Risks of use should be balanced against potential benefits.

Bruton's Tyrosine Kinase Inhibitors

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) due to less off-target activity for other kinases.[13] 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 a retrospective case series of 19 patients with severe COVID-19.[14] However, data interpretation 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* 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 malignancies[9] and prevent chronic graft-versus-host disease in stem cell transplant recipients.[15] Based on results from a small case series, ibrutinib has been theorized to improve inflammation and protect against ensuing lung injury in patients with COVID-19.[16]

Clinical Data for COVID-19

Data regarding ibrutinib are limited to an uncontrolled, retrospective case series of six patients with COVID-19 who were receiving ibrutinib for a condition other than COVID-19.[16] However, evaluation of the data for any clinical benefit is limited by the series's small sample size and lack of a control group.

Clinical Trials

Please check *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.[17] It has been shown to have fewer toxicities than first-generation BTK inhibitors (e.g., ibrutinib) due to less off-target activity for other kinases.[18] Zanubrutinib is proposed to be of use in patients with COVID-19 by modulating signaling that promotes inflammation.

Clinical Data for COVID-19

There is 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.

Janus Kinase Inhibitors

Baricitinib

Baricitinib is an oral JAK inhibitor that is selective for JAK1 and JAK2 and FDA approved for the treatment of rheumatoid arthritis.[19] Among the JAK inhibitors studied, baricitinib has been postulated to have the greatest theoretical antiviral efficacy in inhibiting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from entering and infecting lung cells because of its affinity for adaptor-associated kinase-1 (AAK1), a regulator of viral endocytosis in pulmonary alveolar type 2 (AT2) epithelial cells.[20] In addition, baricitinib can modulate downstream inflammatory responses via inhibition of JAK1/JAK2 kinase and has exhibited dose-dependent inhibition of IL-6-induced STAT3 phosphorylation.[21]

Clinical Data for COVID-19

This study has not been peer-reviewed.

A small, nonrandomized study in patients with moderate COVID-19 pneumonia compared combination therapy with baricitinib and lopinavir/ritonavir to standard of care (SOC) therapy (i.e., combination lopinavir/ritonavir and hydroxychloroquine). Both study groups included 12 patients. Compared to SOC therapy, combination therapy with baricitinib and lopinavir/ritonavir demonstrated a statistically significant shorter time to improvement of clinical and respiratory symptoms and a greater reduction of C-reactive protein levels.[22]

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 and is currently approved for myelofibrosis, polycythemia vera, and acute graft-versus-host disease.[23] Like baricitinib, it is theorized to have antiviral properties through inhibition of AAK1, which may prevent viral entry and infection of pulmonary AT2 epithelial cells.[7]

Clinical Data for COVID-19

A small, prospective, 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 computerized 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 group vs. three deaths [14%] in the control group). 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 frequent concomitant use (among 70% of patients) of antivirals and steroids.[24]

A small, retrospective, single-arm study in Germany reported no safety concerns in 14 patients with severe COVID-19 who received a brief course of ruxolitinib therapy (with a median of 9 days of treatment).[25]

Clinical Trials

Please check [*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 for the treatment of rheumatoid arthritis and has been shown to decrease levels of IL-6 in patients with this disease.[26] Tofacitinib is also FDA approved for the treatment of psoriatic arthritis and ulcerative colitis.[27]

Clinical Data for COVID-19

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

Clinical Trials

Please check [*ClinicalTrials.gov*] for the latest information on studies of tofacitinib and COVID-19.

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Table 3a. Immune-Based Therapy Under Evaluation for the Treatment of COVID-19: Clinical Data to Date

Last Updated: November 3, 2020

Information presented in this table may include data from preprint/non-peer reviewed articles. This table will be updated as new information becomes available.

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on *ClinicalTrials.gov*)
Blood-Derived Products			
COVID-19 Convalescent Plasma	• Convalescent plasma is not approved by the FDA. It has received an EUA from the FDA for the treatment of hospitalized patients with COVID-19.[1] 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.[2,3] 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	• Plasma donated from individuals who have recovered from COVID-19 includes antibodies to SARS-CoV-2.[4] Thousands of U.S. patients have received convalescent plasma through clinical trials, expanded access treatment trials, and EIND applications. However, the standards and methods for screening donated plasma for SARS-CoV-2 binding and neutralizing antibodies have not been established. The variability in SARS-CoV-2 antibody levels in donor plasma may impact the product's efficacy. 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.	**For COVID-19:** • *Open-Label, Randomized Clinical Trial of Convalescent Plasma in 103 Hospitalized Patients With Severe or Life-Threatening COVID-19:* Investigators conducted an open-label, randomized clinical trial of convalescent plasma versus SOC for patients with severe or life-threatening laboratory-confirmed COVID-19 in 7 medical centers in Wuhan, China, from February 14–April 1, 2020. The primary outcome was time to clinical improvement within 28 days, which was defined as patient discharged alive or a reduction of 2 points on a 6-point disease severity scale. Only plasma units with SARS-CoV-2 viral spike-receptor binding domain-specific IgG titer ≥1:640 were transfused. The median dose of ABO-compatible convalescent plasma was 200 mL. The time from symptom onset to randomization was 27 days in the treatment group and 30 days in the control group. Due to control of the COVID-19 outbreak in Wuhan, the trial was terminated early after 103 of the planned for 200 patients were enrolled. The convalescent plasma and control groups were well balanced by age (median age of 70 years vs. 69 years, respectively), but the control group had a higher proportion of men (65%) than the convalescent plasma group (52%). Baseline severity scores (45 patients had severe disease and 58 had life-threatening disease) and use of concomitant therapies were similar between the 2 groups. There was no significant difference between the groups in the primary outcome of 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 23%; OR 1.34; 95% CI, 0.98–1.83; $P = 0.07$). Among those with life-threatening disease, 21% of the convalescent plasma recipients and 24% of the control patients improved by Day 28 (difference -3.4%; OR 0.86; 95% CI, 0.33–2.24; $P = 0.75$). There was no significant difference in 28-day mortality between the groups (16% vs. 24% for the treatment and control groups, respectively; OR 0.65; 95% CI, 0.29–1.46; $P = 0.30$). At 24, 48, and 72 hours, the rates of negative SARS-CoV-2 viral PCR were significantly higher in the convalescent plasma group than in the control group (45% vs. 15%, $P = 0.003$ at 24 hours; 68% vs. 33%, $P = 0.001$ at 48 hours; and 87% vs.

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on [ClinicalTrials.gov](https://clinicaltrials.gov))
Blood-Derived Products, continued			
COVID-19 Convalescent Plasma, continued	to manufacture COVID-19 convalescent plasma in accordance with the Conditions of Authorization set forth in the EUA.		38%, $P < 0.001$ at 72 hours). Two transfusion-related events were reported, including 1 severe event; both events resolved with supportive care. The study's primary limitations were its open-label design and that, on average, the convalescent plasma was transfused approximately 1 month into the disease course. In addition, the study was terminated early, and thus the sample size was insufficient to detect differences in clinical outcomes.[5] • *Open-Label, Randomized, Multicenter Clinical Trial of Convalescent Plasma in Hospitalized Patients with COVID-19 (ConCOVID Study):* An open-label, randomized clinical trial of convalescent plasma versus SOC for hospitalized patients with COVID-19 was conducted in 14 hospitals in the Netherlands from April 8–July 1, 2020. Only plasma confirmed to have anti-SARS-CoV-2 neutralizing antibodies by a SARS-CoV-2 PRNT and a PRNT50 titer ≥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 PRNT, 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. The study was terminated early, and thus lacked sufficient power to detect differences in clinical outcomes between the study groups.[6] • *Open-Label, Randomized, Multicenter Clinical Trial of Convalescent Plasma in Hospitalized Patients with COVID-19 (PLACID Trial): Not Peer Reviewed.* An open-label, randomized clinical trial of convalescent plasma versus SOC for hospitalized patients with COVID-19 was conducted in 39 tertiary care centers in India from April 22–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 PaO_2/FiO_2 <200 mmHg or shock) were excluded. The primary outcome was time to disease progression through 28 days (i.e., to PaO_2/FiO_2 <100 mmHg) or all-cause mortality at 28 days. Participants in the intervention arm received 2 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 SOC arm. The arms were well-balanced with regard to age

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on [ClinicalTrials.gov](https://clinicaltrials.gov))
Blood-Derived Products, continued			
COVID-19 Convalescent Plasma, continued			(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 SOC arm). 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.[7] • *Preliminary Safety Analysis of the First Consecutive 5,000 Patients to Receive Open-Label COVID-19 Convalescent Plasma Through a National Expanded Access Program:*[8] The Expanded Access to Convalescent Plasma for the Treatment of Patients with COVID-19 program was an open-label, nonrandomized protocol primarily designed to provide patients with severe or life-threatening (critical) COVID-19 with access to convalescent plasma, which is an investigational product in the United States. Secondary objectives were to obtain safety data on the product. The protocol was sponsored by the Mayo Clinic and included a diverse range of clinical sites. Plasma donors were required to have documented COVID-19, with complete resolution of symptoms for at least 14 days prior to donation, and be either male, female without history of pregnancy, or female with history of pregnancy and negative HLA testing after the most recent pregnancy. SARS-CoV-2 antibody testing of donors was not mandated. ABO-compatible convalescent plasma was transfused preferentially, but in the absence of ABO-compatible plasma, patients could receive either Group A plasma or low anti-A titer Group O plasma, as available. The Mayo Clinic EAP was discontinued on August 28, 2020. This safety analysis describes the first 5,000 patients, enrolled between April 7–May 3, 2020. Participants were adults with a median age of 62 years; 63% were male and 81% had severe or life-threatening COVID-19. The main safety outcomes for the safety analysis were SAEs including death; SAEs were reported at 4 hours and at 7 days after transfusion, or as they occurred. SAEs were reported in 36 patients (<1%) within 4 hours of transfusion; SAEs included 15 deaths, including 4 possibly or probably related to the convalescent plasma treatment. The 21 nonfatal SAEs included 7 TACO events, 11 TRALI events, and 3 severe allergic reactions. The overall 7-day mortality rate was 14.9%. In this study, COVID-19 convalescent plasma therapy was associated with a low rate (<1%) of serious transfusion-related events. The study design, which does not include a control arm, precludes an assessment of efficacy or ADE. • *Retrospective Exploratory Analyses of Outcomes Among Tens of Thousands of Patients Receiving Open-Label COVID-19 Convalescent Plasma Through the Mayo Clinic EAP:*

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on [ClinicalTrials.gov](https://clinicaltrials.gov))
Blood-Derived Products, continued			

COVID-19 Convalescent Plasma, continued			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.
			• *FDA Efficacy Analysis:* This analysis included 4,330 patients, and donor neutralizing antibody titers were measured by the Broad Institute using a pseudovirus assay.[2] 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 ($P = 0.03$).[1] 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; $P = 0.0008$).[2]
			• *Mayo Clinic Efficacy Analysis: Not Peer Reviewed.* This analysis 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.[9]
			• *Limitations of the EAP Analyses:* 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. In addition:
			  • 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.

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on [ClinicalTrials.gov](https://clinicaltrials.gov))
Blood-Derived Products, continued			
COVID-19 Convalescent Plasma, continued			• 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. • *Retrospective, Single-Center, Case-Control Study Evaluating Convalescent Plasma Plus SOC Versus SOC Without Convalescent Plasma:*[10] *Not Peer Reviewed.* This case-control study reports clinical outcomes among 39 consecutive patients who received COVID-19 convalescent plasma through the FDA's single patient EIND program while hospitalized at Mount Sinai Hospital in New York City during the period of March 24–April 8, 2020. Recipients were transfused with 2 units of ABO-compatible convalescent plasma from donors with a SARS-CoV-2 anti-spike antibody titer of 1:320 dilution. The control group (n = 156) was identified retrospectively from the hospital's EHR database. The control patients were hospitalized during the same period as the patients in the convalescent plasma group and had confirmed COVID-19 but did not receive convalescent plasma. They were matched 4:1 to the convalescent plasma recipients using propensity scores to correct for measured confounders. Convalescent plasma recipients had a mean age of 55 years and 64% were male. At the time of transfusion, 87% of the recipients required supplemental oxygen through noninvasive ventilation and 10% through invasive mechanical ventilation. By Day 14, the clinical condition had worsened in 18% of the convalescent plasma patients and 24% of the control patients ($P = 0.17$). 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% of the transfused patients and 67% of the control patients had been discharged. Interpretation of the study results is limited by the lack of randomization and the potential for unmeasured patient selection bias. • *Retrospective Case-Controlled Study Evaluating Outcomes Among COVID-19 Convalescent Plasma Recipients:* In this 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-

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on [ClinicalTrials.gov](https://clinicaltrials.gov))
Blood-Derived Products, continued			
COVID-19 Convalescent Plasma, continued			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.[10] • *Retrospective Case-Controlled Study of COVID-19 Convalescent Plasma Versus SOC:* This study compared convalescent plasma with SOC in patients with COVID-19 who were hospitalized between March 28 and July 6, 2020, at 8 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 ≥1:1350).[11] • Other smaller, uncontrolled case series describing clinical outcomes in patients with COVID-19 have been reported and also suggest that SAEs are uncommon following COVID-19 convalescent plasma treatment.[12-17]
SARS-CoV-2-Specific Immunoglobulins	• Not approved by the FDA	• 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.	• No clinical data for COVID-19, SARS, or MERS
Non-SARS-CoV-2-Specific Intravenous Immunoglobulins	• Primary immune disorders • Thrombocytopenic purpura • Kawasaki disease • Motor neuropathy	• Currently, only a small proportion of the U.S. population has been infected with SARS-CoV-2. Therefore, products derived from the plasma of donors without confirmation of SARS-CoV-2 infection are not likely to	**For COVID-19:** • *Not Peer Reviewed.* A retrospective, nonrandomized cohort study of IVIG for the treatment of COVID-19 was conducted across 8 treatment centers in China between December 2019 and March 2020. The study found no difference in 28-day or 60-day mortality between 174 patients who were treated with IVIG and 151 patients who were not treated with IVIG. Patients who received IVIG were hospitalized for longer (median stay of 24 days for IVIG group vs. 16 days for no IVIG group) and experienced longer duration of disease (median of 31 days for IVIG group vs. 23 days for no IVIG group).

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on [ClinicalTrials.gov](https://clinicaltrials.gov))
Blood-Derived Products, continued			
Non-SARS-CoV-2-Specific Intravenous Immunoglobulins, continued	• Prophylaxis of various bacterial and viral infections	contain SARS-CoV-2 antibodies. Furthermore, although IVIG contains other blood components that may have general immunomodulatory effects, it is unclear whether these theoretical immunomodulatory effects will benefit patients with COVID-19.	More IVIG-treated patients 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). 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 are difficult to interpret because of important limitations in the study design. In particular, patients were not randomized to receive 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 no IVIG group. The IVIG group also had more patients with severe COVID-19 disease at study entry. Also, patients in both groups received many concomitant therapies for COVID-19.[18]
Mesenchymal Stem Cells	• Not approved by the FDA	• Multipotent adult stem cells that are present in most human tissues including the umbilical cord • It is hypothesized that MSCs could reduce the acute lung injury and inhibit the cell-mediated inflammatory response induced by SARS-COV-2. • MSCs lack the ACE2 receptor that SARS-COV-2 uses for viral entry into cells; therefore, MSCs are resistant to infection.[19,20]	**For COVID-19:** • A pilot study of IV MSC 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 disease. Seven patients (1 with critical illness, 4 with severe illness, and 2 with common-type illness) received MSCs; 3 patients with severe illness received placebo. All 7 patients who received MSCs recovered. Among the 3 severely ill control patients, 1 died, 1 developed ARDS, and 1 remained stable with severe disease.[21] • A small clinical trial evaluated human umbilical cord MSC (hUC-MSC) infusion in patients with severe COVID-19 who had not responded to SOC therapies after 7 to 10 days of treatment. The SOC therapies included supplemental oxygen, umifenovir/oseltamivir, antibiotics if indicated, and glucocorticosteroids. The study was intended as a randomized controlled trial; however, due to the lack of sufficient hUC-MSCs, it was not possible to randomize the participants as originally planned. Among the 41 patients eligible to participate in the study, 12 received hUC-MSC infusion and 29 received SOC therapies only. The study arms were well balanced with regard to demographic characteristics, laboratory test results, and disease severity. All 12 participants who received hUC-MSC infusion recovered without requiring mechanical ventilation and were discharged to home, whereas 4 patients who received only SOC therapies progressed to critical illness requiring mechanical ventilation, and 3 of these patients died. These results are not statistically significant and interpretation of the study is limited by its lack of randomization and small sample size.[22] **For Other Viruses:** • In an open-label study of MSCs for the treatment of H7N9 influenza in China, 17 patients received MSC treatment plus SOC, and 44 patients received SOC only. In the MSC group, 3 patients (17.6%) died; in the control group, 24 patients (54.5%) died.

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on *ClinicalTrials.gov*)
Blood-Derived Products, continued			
Mesenchymal Stem Cells, continued			The 5-year follow-up was limited to 5 patients in the MSC group. No safety concerns were identified.[23]
Immunomodulators			
Corticosteroids			
Dexamethasone	**FDA-Approved Indications:** • Allergic states (e.g., severe or incapacitating asthma, dermatitis, drug HSRs) • Dermatologic diseases (e.g., bullous dermatitis, Stevens-Johnson syndrome) • Endocrine disorders (e.g., adrenocortical insufficiency) • Gastrointestinal diseases (e.g., ulcerative colitis) • Hematologic disorders (e.g., hemolytic anemia, idiopathic thrombocytopenia purpura, pure red cell aplasia) • Neoplastic diseases (e.g., palliative treatment of leukemia, lymphoma) • Nervous system disorders (e.g., multiple sclerosis, cerebral edema) • Ophthalmic diseases (e.g., temporal arteritis, uveitis) • Renal diseases (e.g., to induce diuresis or remission of proteinuria in idiopathic nephrotic syndrome) • Respiratory diseases (e.g., eosinophilic pneumonia)	• Long-acting potent synthetic glucocorticoid with minimal mineralocorticoid activity. Glucocorticoid activity includes anti-inflammatory, immunosuppressive, anti-proliferative, and vasoconstrictive effects.[25] • Potent anti-inflammatory effects may mitigate or prevent the systemic inflammatory response associated with severe COVID-19.	**For COVID-19:** • Please see Corticosteroids for selected clinical data from trials that evaluated dexamethasone for the treatment of COVID-19.

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on [ClinicalTrials.gov](https://www.clinicaltrials.gov))
Immunomodulators			
Corticosteroids			
Dexamethasone, continued	• Rheumatic disorders (e.g., ankylosing spondylitis, rheumatoid arthritis, systemic lupus erythematosus)[24]		
Interferon Alfa and Interferon Beta			
Interferon Alfa	• IFN alfa-2b: Leukemia, melanoma, lymphoma, condylomata acuminata, Kaposi sarcoma, hepatitis B, hepatitis C • IFN alfa-1b is not available in the United States.	• Elicits antiviral, antiproliferative, and immunomodulatory activities on numerous cell types[26-28]	**For COVID-19:** • *Not Peer Reviewed.* In a retrospective cohort study of 77 adults with moderate COVID-19 in China, those who used nebulized IFN alfa-2b with or without umifenovir (Arbidol) achieved viral clearance in the upper respiratory tract faster and had lower systemic inflammation than those who used only umifenovir. However, results are difficult to interpret because participants in the IFN alfa-2b group were substantially younger than those in the umifenovir-only group (mean age 40 years vs. 65 years) and had fewer comorbidities (15% vs. 54%) at study entry. The nebulized formulation of IFN alfa-2b is not FDA approved for use in the United States.[29] • *Press Release.* A double-blind, placebo-controlled trial conducted in the United Kingdom evaluated inhaled IFN 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 IFN 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. Note that the inhaled IFN beta-1a formulation used in this study is not commercially available in the United States.[30] • An open-label, randomized trial at a single center in Iran evaluated SQ IFN beta-1a (3 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 IFN beta-1a group (n = 42) and the control group (n = 39), and there was no difference between the groups in overall length of hospitalization, length of ICU stay, or duration of mechanical ventilation. The reported 28-day overall mortality was lower in the IFN beta-1a group, but 4 patients in that group who died before receiving the fourth dose of IFN beta-1a were excluded from the analysis, which makes it difficult to interpret these results.[31]
Interferon Beta	• Multiple sclerosis (IFN beta-1a, IFN beta-1b)	• Elicits antiviral, antiproliferative, and immunomodulatory activities on numerous cell types (T cell, B cell, and cytokine function)[26,33] • Among IFN subtypes, IFN beta-1b shows greatest in vitro inhibition of MERS-CoV.[34,35] • In vitro activity against MERS-CoV in lung cells.[36]	

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on [ClinicalTrials.gov](https://clinicaltrials.gov))
Interferon Alfa and Interferon Beta, continued			
Interferon Alfa	• IFN alfa-2b: Leukemia, melanoma, lymphoma, condylomata acuminata, Kaposi sarcoma, hepatitis B, hepatitis C • IFN alfa-1b is not available in the United States.	• Elicits antiviral, antiproliferative, and immunomodulatory activities on numerous cell types[26-28]	• An open-label, Phase 2 clinical trial randomized 127 participants (median age 52 years) 2:1 to combination antiviral therapy or LPV/r. In the combination antiviral therapy group, the treatment regimen differed by time from symptom onset to hospital admission. Participants admitted within 7 days of symptom onset (n = 76) were randomized to triple drug therapy (IFN beta-1b 8 million international units SQ every other day for up to 7 days total, LPV/r, and ribavirin); those admitted ≥7 days after symptom onset (n = 51) were randomized to double therapy (LPV/r and ribavirin) because of concerns regarding potential inflammatory effects of IFN. All participants in the control group received LPV/r alone regardless of time from symptom onset to hospitalization. The study participants were patients in Hong Kong with confirmed SARS-CoV-2 infection who were hospitalized regardless of disease severity until they had 2 negative NP swabs. The median time to a negative SARS-CoV-2 PCR on an NP swab (the primary endpoint) was shorter for the combination group than for the control group (7 days vs. 12 days, $P = 0.001$). The combination group had more rapid clinical improvement as assessed by NEWS2 and SOFA score and a shorter hospital stay (9 days for combination group vs. 14.5 days for 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 IFN beta-1b with or without ribavirin was the critical component of the combination therapy. The study provides no information about the effect of IFN beta-1b administered ≥7 days after symptom onset.[32]
Interferon Beta	• Multiple sclerosis (IFN beta-1a, IFN beta-1b)	• Elicits antiviral, antiproliferative, and immunomodulatory activities on numerous cell types (T cell, B cell, and cytokine function)[26,33] • Among IFN subtypes, IFN beta-1b shows greatest in vitro inhibition of MERS-CoV.[34,35] • In vitro activity against MERS-CoV in lung cells.[36]	

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on [ClinicalTrials.gov](https://clinicaltrials.gov))
Interleukin-1 Inhibitor			
Anakinra	• Rheumatoid arthritis • Cryopyrin-associated periodic syndromes, specifically neonatal-onset multisystem inflammatory disease[37] • IV formulation is not approved for use in the United States.	• Competitively inhibits IL-1 binding to the IL-1 type I receptor	**For COVID-19:** • A case-control study compared outcomes in 52 consecutive patients with COVID-19 treated with anakinra to outcomes in 44 historical controls. The patients in both groups were admitted to the same hospital system in Paris, France. Cases were consecutive admissions from March 24–April 6, 2020, with laboratory-confirmed SARS-CoV-2 infection or lung infiltrates on chest imaging typical of COVID-19, and either significant hypoxia (SpO_2 ≤93% with ≥6 L/min O_2) or worsening hypoxia (SpO_2 ≤93% with >3 L/min O_2 and a loss of ≥3% of O_2 saturation on room air in the previous 24 hours). Historic controls were patients fulfilling the same eligibility criteria and admitted to the hospital from March 18–March 24, 2020. SOC for both groups entailed use of HCQ, AZM, and parenteral beta-lactam antibiotics. Patients in the anakinra group received anakinra 100 mg SQ twice daily for 72 hours, followed by anakinra 100 mg daily for 7 days. Clinical characteristics were similar between the groups, except that the case patients had a lower mean BMI (25.5 kg/m^2 for cases vs. 29.0 kg/m^2 for controls), longer duration of symptoms (8.4 days for cases vs. 6.2 days for controls), and a higher frequency of HCQ use (90% for cases vs. 61% for controls) and AZM use (49% for cases vs. 34% for controls). The primary outcome of either admission to the ICU for invasive mechanical ventilation or death occurred among 13 cases (25%) and 32 controls (73%) (HR 0.22; 95% CI, 0.11–0.41). However, within the first 2 days of follow up in the control group, 6 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. CRP levels decreased by Day 4 among those receiving anakinra. Thromboembolic events occurred in 10 patients (19%) in the case group and 5 patients (11%) in the control group. 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.[38] • A single-center case series reported on open-label use of anakinra in 9 hospitalized patients with COVID-19, presenting with 4–12 days of symptoms, requiring oxygen ≤6 L/min, and serum CRP ≥50 mg/L. Anakinra was administered SQ, 100 mg every 12 hours for 3 days followed by 100 mg daily for up to 7 more days. Two patients also received HCQ plus AZM; the other 7 patients received no specific additional treatments. Anakinra was discontinued in 1 patient who progressed to acute respiratory failure after

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on [ClinicalTrials.gov](https://clinicaltrials.gov))
Interleukin-1 Inhibitor, continued			
Anakinra, continued			the first dose of the drug. Good clinical outcomes were observed in the other 8 patients as assessed by oxygen flow, decline in CRP, and no progression in infiltrates on serial CT scans. Three patients had elevated liver transaminase levels. Results are difficult to interpret because of the low number of patients in the case series, the short follow-up, and the absence of a comparison group.[39] • A single-center, retrospective, cohort study in Italy compared outcomes in 29 patients following open-label anakinra use with outcomes in 16 historical controls. All patients had COVID-19 with moderate to severe ARDS requiring noninvasive ventilation and evidence of hyperinflammation. High-dose IV anakinra 5 mg/kg twice daily was administered for a median of 9 days, followed by SQ administration (anakinra 100 mg twice daily) for 3 days to avoid inflammatory relapses. Both the anakinra and control (standard treatment) groups received HCQ and LPV/r. In the high-dose anakinra group, reductions in CRP levels were noted following anakinra initiation. The 21-day survival rate was 90% in the anakinra group and 56% in the control group ($P = 0.009$); however, the patients in the anakinra group were younger (median age of 62 years in anakinra group vs. 70 years in control group), and fewer patients had chronic kidney disease. High-dose anakinra was discontinued in 7 patients (24%) due to AEs (bacteremia in 4 patients, elevated liver enzymes in 3 patients); however, retrospective assessment showed that these events occurred with similar frequency in the control group. An additional group of 7 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.[40]

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on *ClinicalTrials.gov*)
Interleukin-6 Inhibitors Elevations in IL-6 levels may be an important mediator when severe systemic inflammatory responses occur in some patients with COVID-19; IL-6 inhibition may reduce these effects.			
Sarilumab	• Rheumatoid arthritis[41]	• Human recombinant monoclonal antibody • IL-6 receptor antagonist[42]	**For COVID-19:** • *Press Release:* In a Phase 2 and 3 clinical trial (*ClinicalTrials.gov* Identifier NCT04315298), patients hospitalized with COVID-19 were randomized (2:2:1) to receive sarilumab 400 mg, sarilumab 200 mg, or placebo. 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 7-point 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. 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.[43]
Siltuximab	• Multicentric Castleman disease	• Recombinant human-mouse chimeric monoclonal antibody • IL-6 antagonist[44]	**For COVID-19:** • *Not Peer Reviewed.* In a single-center observational study of 21 patients with COVID-19 who developed pneumonia and ARDS and received treatment with IV siltuximab, some patients experienced decreased CRP levels (16 of 21 patients) and improved clinical condition (7 of 21 patients) following siltuximab treatment. Other patients experienced no clinically relevant change in condition (9 of 21 patients) or worsening condition (5 of 21 patients). Among the 5 patients with worsening condition, there was 1 death and 1 cerebrovascular event (median follow-up of 8 days).[45]

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on [ClinicalTrials.gov](https://clinicaltrials.gov))
Interleukin-6 Inhibitors, continued			
Tocilizumab	• Cytokine release syndrome (induced by CAR T-cell therapy) • Rheumatoid arthritis • Giant cell arteritis • Polyarticular juvenile idiopathic arthritis • Systemic juvenile idiopathic arthritis[46]	• Recombinant humanized monoclonal antibody • IL-6 receptor antagonist	**For COVID-19:** • *Press Release:* The industry-sponsored Phase 3 COVACTA trial (*ClinicalTrials.gov* Identifier NCT04320615) randomized 450 adults hospitalized with severe COVID-19-related pneumonia 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 7-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.[47] • *Press Release:* Early results were reported for the CORIMUNO-TOCI trial (*ClinicalTrials.gov* Identifier NCT04331808), an open-label, randomized trial of hospitalized patients with COVID-19 (n = 129) at 7 sites in France. The patients, who had moderate or severe disease at study entry, were randomized to receive tocilizumab plus SOC (n = 65) or SOC alone (n = 64). The dosing strategy was tocilizumab 8 mg/kg on Day 1; if there was no response (i.e., no decrease of oxygen requirement), a second infusion was repeated on Day 3. In this preliminary report, the proportion of participants who died or needed ventilation (noninvasive or mechanical) was lower in the tocilizumab group than in the SOC alone group. Detailed results of the trial have not been reported. • Sixty-three adults hospitalized with COVID-19 were enrolled in a prospective open-label study of tocilizumab for severe COVID-19. All patients received off-label ARV PIs. Patients received either tocilizumab 8 mg/kg IV or tocilizumab 324 mg SQ; within 24 hours, a second dose of tocilizumab was administered to 52 of the 63 patients. Following tocilizumab administration, fevers resolved in all but 1 patient, and CRP, ferritin, and D-dimer levels declined. The mean PaO_2/FiO_2 ratio

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on [ClinicalTrials.gov](https://clinicaltrials.gov))
Interleukin-6 Inhibitors, continued			
Tocilizumab, continued			increased between admission (152 +/-53 mm Hg) and Day 7 (284 +/-116 mm Hg). No moderate or severe AEs attributable to tocilizumab were reported. Overall mortality rate was 11% (7 deaths among the 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, but provide no details regarding a comparison group or specify an a priori comparison, which limits interpretation of this result.[48] • An uncontrolled, retrospective cohort study of 21 hospitalized COVID-19 patients who received tocilizumab reported improvement in oxygenation and systemic inflammation. At study entry, among the 21 patients (mean age 56 years; range 25 to 88 years), 17 had severe disease and 4 had critical disease. All patients were febrile, had abnormal chest CT findings, and required oxygen supplementation (2 required mechanical ventilation). Mean CRP level was 75 mg/L, mean IL-6 expression level was 153 pg/mL, mean D-dimer level was 0.80 μg/mL, and mean lymphocyte percentage was 15.5%. Eighteen patients were given tocilizumab IV infusion once, and within 12 hours, 3 patients received a second infusion for indication of fever. Following tocilizumab administration, fevers normalized, lymphocyte percentages improved, and CRP levels declined. By Day 5, oxygen requirements were reduced in 15 of 20 participants (75%). There were no serious AEs attributed to tocilizumab, and no concurrent bacterial, fungal, or viral infections were observed during the treatment. The interpretability of this retrospective case series is limited due to its small sample size and lack of control group.[49] • Additional data supporting the use of tocilizumab for COVID-19 include a small retrospective cohort study, a case series, and a case-control study.[50-52]
Kinase Inhibitors			
Bruton's Tyrosine Kinase Inhibitors			
Acalabrutinib	• Chronic lymphocytic leukemia/small lymphocytic lymphoma • Mantle cell lymphoma[53]	• Second-generation oral BTK inhibitor • Inhibits BTK signaling of the B-cell antigen receptor and cytokine receptor pathways • Potential modulation of signaling that promotes inflammation and cytokine storm[54]	**For COVID-19:** • Data regarding acalabrutinib are limited to a retrospective case series in 19 patients with severe COVID-19. However, data interpretation to discern any clinical benefit is limited by the study's small sample size and lack of a control group.[55]

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on [ClinicalTrials.gov](https://www.clinicaltrials.gov))
Bruton's Tyrosine Kinase Inhibitors, continued			
Ibrutinib	• Chronic lymphocytic leukemia/ small lymphocytic lymphoma • Mantle cell lymphoma • Marginal zone lymphoma • Waldenström macroglobulinemia • Chronic graft-versus-host disease in stem cell transplant recipients[56]	• First-generation oral BTK inhibitor • Inhibits BTK signaling of the B-cell antigen receptor and cytokine receptor pathways • Potential modulation of signaling that promotes inflammation and cytokine storm[57]	**For COVID-19:** • Data regarding ibrutinib are limited to an uncontrolled, retrospective case series of 6 patients with COVID-19 who were receiving ibrutinib for a condition other than COVID-19. However, evaluation of the data for any clinical benefit is limited by the study's small sample size and lack of control group.[57]
Zanubrutinib	• Mantle cell lymphoma[58]	• Second-generation oral BTK inhibitor • Inhibits BTK signaling of the B-cell antigen receptor and cytokine receptor pathways • Potential modulation of signaling that promotes inflammation and cytokine storm[54]	• No clinical data for COVID-19, SARS, or MERS
Janus Kinase Inhibitors			
Baricitinib	• Rheumatoid arthritis[59]	• JAK inhibitor selective for JAK1, JAK2, and TYK2, relative to JAK3 • Theoretical direct antiviral activity through inhibition of kinases (AAK1 and cyclin G-associated kinase) that regulate viral endocytosis in pulmonary AT2 epithelial cells, which may prevent SARS-CoV-2 entry into and infection of susceptible cells. • Dose-dependent inhibition of IL-6 induced STAT3 phosphorylation[60]	**For COVID-19:** • *Not Peer Reviewed.* A small, nonrandomized study of 12 patients with moderate COVID-19 pneumonia compared therapy with baricitinib and LPV/r with SOC alone (i.e., combination LPV/r and HCQ).[61] Baricitinib and LPV/r therapy demonstrated a statistically significant time to improvement in clinical and respiratory symptoms and reduction in measured CRP.[61]

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
Janus Kinase Inhibitors, continued			
Ruxolitinib	• Myelofibrosis • Polycythemia vera • Steroid-refractory acute graft-versus-host disease[62]	• JAK inhibitor selective for JAK1 and JAK2 • Theoretical antiviral properties through inhibition of AAK1 which may prevent viral entry into and infection of pulmonary AT2 alveolar epithelial cells[63,64] • Inhibition of IL-6 via JAK1/JAK2 pathway inhibition	**For COVID-19:** • A small, prospective, single-blind randomized controlled Phase 2 trial in patients with COVID-19 in China compared ruxolitinib 5 mg PO twice daily (n = 20) to placebo (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 2 arms. Treatment with ruxolitinib was associated with a nonsignificant reduction in median time to clinical improvement (12 days for ruxolitinib vs. 15 days for placebo; *P* = 0.15), defined as a 2-point improvement on a 7-category ordinal scale or 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 CT 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 when present (5 days for ruxolitinib vs. 8 days for placebo; *P* = 0.03). The use of ruxolitinib was not associated with an increased risk of AEs or mortality (no deaths in the ruxolitinib group vs. 3 deaths [14% of patients] in the control group). Despite the theoretical antiviral properties of JAK inhibitors, there was no significant difference in time to viral clearance among patients who had detectable viral loads at randomization to ruxolitinib (n = 8) or placebo (n = 9). Limitations of this study include the small sample size, the exclusion of patients who required invasive mechanical ventilation at study entry, and the concomitant use of antivirals and steroids by 70% of patients.[65] • A small, retrospective, single-arm study in Germany reported no safety concerns in 14 patients with severe COVID-19 who received a brief course of ruxolitinib therapy (median 9 days).[66]
Tofacitinib	• Rheumatoid arthritis • Psoriatic arthritis • Ulcerative colitis[67]	• JAK inhibitor selective for JAK1 and JAK3 with modest activity against JAK2 • Blocks signaling from gamma-chain cytokines (IL-2, IL-4) and gp130 proteins (IL-6, IL-11, IFNs) • Shown to decrease levels of IL-6 in rheumatoid arthritis[68]	• No clinical data for COVID-19, SARS, or MERS

Key: AAK1 = Adaptor-associated kinase 1; ADE = antibody-dependent enhancement; AE = adverse event; ARDS = acute respiratory distress syndrome; ARV = antiretroviral; AT2 = alveolar type 2; AZM = azithromycin; BTK = Bruton's tyrosine kinase; CAR = chimeric antigen receptor; CRP = C-reactive protein; CI = confidence interval; CT = computerized tomography; EHR = electronic health record; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; GAK = cyclin G-associated kinase; HCQ = hydroxychloroquine; HR = hazard ratio; HSR = hypersensitivity reaction; ICU = intensive care unit; IDMC = independent data monitoring committee; IFN = interferon; IL = interleukin; IND = Investigational New Drug application; IV = intravenous; IVIG = intravenous immune globulin; LPV/r = lopinavir/ritonavir; JAK = Janus kinase inhibitor; MERS = Middle East respiratory syndrome; MERS-CoV = Middle East respiratory syndrome coronavirus; MSC = mesenchymal stem cells; NP = nasopharyngeal; NEWS2 = National Early Warning Score 2; OR = odds ratio; PaO_2/FiO_2 = ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; PCR = polymerase chain reaction; PI = protease inhibitor; PRNT = plaque reduction neutralization test; RR = age-adjusted rate ratio; SAE = adverse event; SARS = severe acute respiratory syndrome; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOC = standard of care; SOFA = sequential organ failure assessment; SQ = subcutaneous; STAT3 = signal transducer and activator of transcription 3; TACO = transfusion-associated circulatory overload, TRALI = transfusion-related acute lung injury

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Table 3b. Characteristics of Immune-Based Therapy Under Evaluation for the Treatment of COVID-19

Last Updated: November 3, 2020

- The information in this table is derived from data on the use of these drugs and biologic products for FDA-approved indications or in investigational trials; it is supplemented with data on their use in patients with COVID-19, when available.
- The effective dosing of these agents for the treatment of COVID-19 is unknown. Therefore, the doses listed below are primarily derived from FDA-approved indications or from clinical trials that are investigating therapies for COVID-19.
- 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.
- Treatment-related AEs associated with immune-based therapy in patients with COVID-19 are not well defined. Whether the frequency and severity of AEs associated with use of these agents for FDA approved-indications are the same in patients with COVID-19, especially in critically ill patients, is unknown. AEs associated with long-term use of these drugs (i.e., months to years) are not included in this table because treatment for COVID-19 is not long term. 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 additional safety monitoring.
- The potential additive, antagonistic, or synergistic effects and the safety of 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 labeling and visit the Liverpool COVID-19 Drug Interactions website.
- For information on drugs that prolong the QTc interval, please visit CredibleMeds.org.

Drug Name	**Dosing Regimen** *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.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Blood-Derived Products					
COVID-19 Convalescent Plasma	1 or more transfusions based on patient response	• TRALI • TACO • Allergic reactions • Antibody-mediated enhancement of infection • Red cell alloimmunization • Transmission of infectious pathogens[1] • Thrombotic events	• Monitor for transfusion-related reactions. • Vital signs at baseline and during and after transfusion	Drug products **should not be added** to the IV infusion line for the blood product.	• 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: Convalescent Plasma
Immunoglobulins: SARS-CoV-2 Specific	Doses vary by clinical trial.	• TRALI • TACO • Allergic reactions • Antibody-mediated enhancement of infection • Red cell alloimmunization • Transmission of infectious pathogens	• Monitor for transfusion-related reactions. • Vital signs at baseline and during and after transfusion	Drug products **should not be added** to the IV infusion line for the blood product.	• 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: Immunoglobulin

Drug Name	**Dosing Regimen** *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.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Blood-Derived Products, continued					
Immunoglobulins: Non-SARS-CoV-2 Specific	Doses vary based on indication and formulation.	• Allergic reactions including anaphylaxis • Renal failure • Thrombotic events • Aseptic meningitis syndrome • Hemolysis • TRALI • Transmission of infectious pathogens	• Monitor for transfusion-related reactions. • Vital signs at baseline and during and after infusion • Discontinue if renal function deteriorates during treatment.	IVIG may interfere with immune response to certain vaccines.	• 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. • AEs may vary by formulation. • AEs may be precipitated by high-dose, rapid infusion, or underlying conditions. • A list of clinical trials is available: Intravenous Immunoglobulin
Mesenchymal Stem Cells	Doses vary by clinical trial. In the United States, mesenchymal stem cells **should not be used** in the United States for the treatment of COVID-19 outside of an FDA-approved clinical trial, expanded access protocol, or EIND process.	• Failure of the cells to work as expected[2] • Potential for mesenchymal stem cells to multiply or change into inappropriate cell types • Product contamination • Growth of tumors • Infections • Thrombus formation[3] • Administration site reactions[4,5]	• Monitor for administration site reactions.	Drug products **should not be added** to the IV infusion line for the mesenchymal stem cell product.	• The Panel **recommends against** the use of mesenchymal stem cells for the treatment of COVID-19, except in a clinical trial **(AII)**. • The FDA has issued several warnings about patients being potentially vulnerable to stem cell treatments that are illegal and potentially harmful.[4] A number of cord blood-derived products are currently licensed by the FDA for various indications such as the treatment of cancer (stem cell transplant) and rare genetic diseases. These products are not FDA approved for the treatment of COVID-19. • A list of clinical trials is available: Mesenchymal Stem Cells

Drug Name	**Dosing Regimen** *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.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Immunomodulators					
Corticosteroids					
Dexamethasone	**For COVID-19:** • Dexamethasone 6 mg daily IV or PO, for up to 10 days[6] • Dexamethasone should be continued for up to 10 days or until hospital discharge, whichever comes first.	• Hyperglycemia • Secondary infections • Reactivation of latent infections (e.g., HBV, HSV, strongyloidiasis, TB) • Psychiatric disturbances • Avascular necrosis • Adrenal insufficiency • Increased blood pressure • 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.[7,8]	• Blood glucose • Blood pressure • Signs and symptoms of new infection • 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 who engage in agricultural activities) or fulminant reactivations of HBV should be considered.[9-11]	• 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).	For the Panel's recommendations on the use of corticosteroids, please see Therapeutic Management of Patients with COVID-19. • If dexamethasone is not available, an alternative corticosteroid such as **prednisone**, **methylprednisolone**, or **hydrocortisone** can be used **(BIII)**. • The approximate total daily dose equivalencies for these glucocorticoids to dexamethasone 6 mg (PO or IV) are: prednisone 40 mg, methylprednisolone 32 mg, and hydrocortisone 160 mg. • A list of clinical trials is available: Dexamethasone

Drug Name	**Dosing Regimen** *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.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Interferons					
Interferon Alfa	• Peginterferon alfa-2a 180 mcg SQ once weekly for 2 weeks for MERS[12,13] **IFN Alfa-2b:** *COVID-19 Clinical Trial Dosing:* • Nebulized IFN alfa-2b 5 million international units twice daily (no duration listed in the study)[14]	• Flu-like symptoms (e.g., fever, fatigue, myalgia)[15] • Injection site reactions • Liver function abnormalities • Decreased blood counts • Worsening depression • Insomnia • Irritability • Nausea • Vomiting • Hypertension • Induction of autoimmunity	• CBC with differential • Liver enzymes; avoid if Child-Pugh Score >6 • Depression, psychiatric symptoms • Reduce dose in patients with CrCl <30 mL/min.	• Low potential for drug interactions • Inhibition of CYP1A2	• 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. • Nebulized IFN alfa-2b is not approved by the FDA for use in the United States. • IFN alfa-1b is not approved by the FDA for use in the United States. • Use with caution with other hepatotoxic agents. • Reduce dose if ALT >5 times ULN; discontinue if accompanied by an increase in bilirubin level. • Reduce dose or discontinue if neutropenia or thrombocytopenia occur. • A list of clinical trials is available: Interferon

Drug Name	**Dosing Regimen** *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.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Interferons, continued					
Interferon Beta	**IFN Beta-1a:** • IFN beta-1a 44 mcg SQ 3 times weekly for MERS[13] • Duration for COVID-19 unknown **IFN Beta-1b:** • IFN beta-1b 8 million international units SQ, every other day, up to 7 days total for COVID-19[16]	• Flu-like symptoms (e.g., fever, fatigue, myalgia)[17] • Leukopenia, neutropenia, thrombocytopenia, lymphopenia • Liver function abnormalities (ALT > AST) • Injection site reactions • Headache • Hypertonia • Pain • Rash • Worsening depression • Induction of autoimmunity	• Liver enzymes • CBC with differential • Worsening CHF • Depression, suicidal ideation	Low potential for drug interactions	• 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)**. • 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 and 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 **Availability:** • Several products are available in the United States; product doses differ. *IFN Beta-1a Products:* • Avonex, Rebif *IFN Beta-1b Products:* • Betaseron, Extavia

Drug Name	**Dosing Regimen** *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.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Interleukin-1 Inhibitor					
Anakinra	• Standard adult dose is anakinra 100 mg SQ once daily • Has also been used IV • Duration for COVID-19 unknown	• Neutropenia (particularly in combination with other agents that can cause neutropenia) • Anaphylaxis • Headache, nausea, diarrhea, sinusitis, arthralgia, flu-like symptoms, and abdominal pain • Injection site reactions • Liver enzyme elevations	• CBC with differential • Renal function (reduce dose in patients with CrCl <30 mL/min) • Liver enzymes	Use with TNF-blocking agents **is not recommended** due to increased risk of infection.	• 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					
Anti-Interleukin-6 Receptor Monoclonal Antibodies					
Sarilumab[18]	**Clinical Trial Dosing (See *ClinicalTrials.gov* Identifier NCT04315298):** • Sarilumab 400 mg IV (single dose)[19] **Note:** The only FDA-approved sarilumab product is an SQ formulation.	• Neutropenia, thrombocytopenia • Gastrointestinal perforation • HSR • Increased liver enzymes • HBV reactivation • Infusion reaction possible	• Monitor for HSR • Monitor for infusion reaction • Neutrophils • Platelets • Liver enzymes	• Elevated IL-6 may downregulate CYP enzymes; use of sarilumab may lead to increased metabolism of drugs that are CYP450 substrates. • Effects on CYP450 may persist for weeks after therapy.	• The Panel **recommends against** the use of sarilumab for the treatment of COVID-19, except in a clinical trial **(BI)**. • May mask signs of acute inflammation or infection (i.e., suppression of fever and CRP) • A list of clinical trials is available: Sarilumab

Drug Name	**Dosing Regimen** *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.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Anti-Interleukin-6 Receptor Monoclonal Antibodies, continued					
Tocilizumab[20]	**Clinical Trial Dosing:** • Tocilizumab 8 mg/kg IV once • Dose **should not exceed** tocilizumab 800 mg. • Dose may be repeated once, 12 hours later, if clinical symptoms worsen or show no improvement (see *ClinicalTrials.gov* Identifier NCT04320615).	• Infusion-related reactions • HSR • Gastrointestinal perforation • Hepatotoxicity • Treatment-related changes in neutrophils, platelets, lipids, and liver enzymes • HBV reactivation	• Monitor for HSR • Monitor for infusion reactions • Neutrophils • Platelets • Liver enzymes	• 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.	• The Panel **recommends against** the use of tocilizumab for the treatment of COVID-19, except in a clinical trial **(BI)**. • May mask signs of acute inflammation or infection (i.e., suppression of fever and CRP) • The SQ formulation of tocilizumab **is not intended** for IV administration. • A list of clinical trials is available: Tocilizumab
Anti-Interleukin-6 Monoclonal Antibody					
Siltuximab	• Siltuximab 11 mg/kg administered over 1 hour by IV infusion every 3 weeks for multicentric Castleman disease[21] • Dose and duration for COVID-19 unknown	• Infusion-related reaction • HSR • Gastrointestinal perforation • Neutropenia • Hypertension • Dizziness • Rash • Pruritus • Hyperuricemia	• Monitor for HSR • Monitor for infusion reaction • Neutrophils	• 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.	• The Panel **recommends against** the use of siltuximab for the treatment of COVID-19, except in a clinical trial **(BI)**. • May mask signs of acute inflammation or infection (i.e., suppression of fever and CRP) • A list of clinical trials is available: Siltuximab

Drug Name	**Dosing Regimen** *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.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Kinase Inhibitors					
Bruton's Tyrosine Kinase Inhibitors					
Acalabrutinib	**Dose for FDA-Approved Indications:** • Acalabrutinib 100 mg PO every 12 hours • Dose and duration for COVID-19 unknown	• Hemorrhage • Cytopenias (neutropenia, anemia, thrombocytopenia, lymphopenia) • Atrial fibrillation and flutter • Infection • Headache • Diarrhea • Fatigue • Myalgia	• CBC with differential • Signs and symptoms of bleeding (particularly when coadministered with anticoagulant or antiplatelet therapy) • Monitor for cardiac arrhythmias • Monitor for new infections	• 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.	• 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 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
Ibrutinib	**Doses for FDA-Approved Indications:** • Ibrutinib 420 mg or 560 mg PO once daily • Dose and duration for COVID-19 unknown	• Hemorrhage • Cardiac arrhythmias • Serious infections • Cytopenias (thrombocytopenia, neutropenia, anemia) • Hypertension • Diarrhea • Musculoskeletal pain • Rash	• 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	• Avoid concomitant use with strong CYP3A inhibitors or inducers. • Dose reduction may be necessary with moderate CYP3A4 inhibitors.	• The Panel **recommends against** the use of BTK inhibitors for the treatment of COVID-19, except in a clinical trial **(AIII)**. • Avoid 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

Drug Name	**Dosing Regimen** *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.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Bruton's Tyrosine Kinase Inhibitors, continued					
Zanubrutinib	**Dose for FDA-Approved Indications:** • Zanubrutinib 160 mg PO twice daily or 320 mg PO once daily • Dose and duration for COVID-19 unknown	• Hemorrhage • Cytopenias (neutropenia, thrombocytopenia, anemia, leukopenia) • Atrial fibrillation and flutter • Infection • Rash • Bruising • Diarrhea • Cough • Musculoskeletal pain	• CBC with differential • Signs and symptoms of bleeding • Monitor for cardiac arrhythmias • Monitor for new infections	• **Avoid** concomitant use with moderate or strong CYP3A inducers. • Dose reduction required with moderate and strong CYP3A4 inhibitors.	• 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
Janus Kinase Inhibitors					
Baricitinib[22]	**For Rheumatoid Arthritis:** • Baricitinib 2 mg PO once daily **Doses for COVID-19 in Clinical Trials:** • Baricitinib 2–4 mg PO once daily for 7–14 days	• Lymphoma and other malignancies • Thrombosis • Gastrointestinal perforation • Treatment-related changes in lymphocytes, neutrophils, hemoglobin, liver enzymes • Herpes simplex • Herpes zoster	• CBC with differential • Renal function • Liver enzymes • Monitor for new infections	Dose modification is recommended when concurrently administering with a strong OAT3 inhibitor.	• The Panel **recommends against** the use of JAK inhibitors for the treatment of COVID-19, except in a clinical trial **(AIII)**. • Baricitinib **is not recommended** in patients with severe hepatic or renal impairment. • A list of clinical trials is available: Baricitinib

Drug Name	**Dosing Regimen** *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.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Janus Kinase Inhibitors, continued					
Ruxolitinib	• Doses for FDA-approved indications range from ruxolitinib 5 mg PO twice daily to 20 mg PO twice daily. • Doses in COVID-19 clinical trials range from ruxolitinib 5 mg PO twice daily to 20 mg PO twice daily, for 14 days.	• Thrombocytopenia • Anemia • Neutropenia • Liver enzyme elevations • Risk of infection • Dizziness • Headache • Diarrhea • CPK elevation • Herpes zoster	• CBC with differential • Liver enzymes • Monitor for new infections	• Dose modifications required when administered with strong CYP3A4 inhibitors. • **Avoid** use with fluconazole doses >200 mg.	• The Panel **recommends against** the use of JAK inhibitors 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
Tofacitinib	**Doses for FDA-Approved Indications:** • Tofacitinib 5 mg PO twice daily (rheumatoid and psoriatic arthritis) • Tofacitinib 10 mg PO twice daily (ulcerative colitis) • Dose and duration for COVID-19 is unknown; a planned COVID-19 clinical trial will be evaluating tofacitinib 10 mg twice daily for 14 days.	• Thrombotic events (pulmonary embolism, DVT, arterial thrombosis) • Anemia • Risk of infection • Gastrointestinal perforation • Diarrhea • Headache • Herpes zoster reactivation • Lipid elevations • Liver enzyme elevations • Lymphoma and other malignancies	• CBC with differential • Liver enzymes • Monitor for new infections.	• 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.	• The Panel **recommends against** the use of JAK inhibitors for the treatment of COVID-19, except in a clinical trial **(AIII)**. • Avoid use in patients with ALC <500 cells/mm^3, ANC <1,000 cells/mm^3, 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

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; FDA = Food and Drug Administration; 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; PK = pharmacokinetic; PO = orally; PPI = proton pump inhibitor; 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

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Adjunctive Therapy

Last Updated: July 17, 2020

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

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

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

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

Antithrombotic Therapy in Patients with COVID-19

Last Updated: December 17, 2020

Summary Recommendations

Laboratory Testing

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

Chronic Anticoagulant and Antiplatelet Therapy

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

Venous Thromboembolism Prophylaxis and Screening

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

Hospitalized Children With COVID-19

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

Treatment

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

Special Considerations During Pregnancy and Lactation

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

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

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

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

Association Between COVID-19 and Thromboembolism

Infection with the novel severe acute respiratory syndrome coronavirus (SARS-CoV-2) and the resulting syndrome, COVID-19, has been associated with inflammation and a prothrombotic state, with increases in fibrin, fibrin degradation products, fibrinogen, and D-dimers.[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 septic patients 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.

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

There are limited prospective data demonstrating the safety and efficacy of using therapeutic doses of anticoagulants in patients with COVID-19 to prevent VTE. A retrospective analysis of 2,773 hospitalized COVID-19 patients from a single center in the United States reported in-hospital mortality in 22.5% of patients who received therapeutic anticoagulation and 22.8% of patients who did not receive anticoagulation. The study further reported that in a subset of 395 mechanically ventilated patients, 29.1% who received anticoagulation and 62.7% who did not receive anticoagulation died. The study had important limitations: it lacked details on patient characteristics, indications for anticoagulant initiation, and descriptions of other therapies that the patients received that may have influenced mortality. In addition, the authors did not discuss the potential impact of survival bias on the study results. For these reasons, the data are not sufficient to influence standard of care, and this study further emphasizes the need for prospective trials to define the risks and potential benefits of therapeutic anticoagulation in patients with COVID-19.[18]

A small, single-center, randomized trial of 20 patients compared therapeutic and prophylactic anticoagulation in mechanically ventilated patients with D-dimers >1,000 µg/L (as measured by the VIDAS D-dimer Exclusion II assay). Only the patients treated with therapeutic anticoagulation showed improvement in PaO_2:FiO_2 ratio. The number of ventilator-free days was higher in the therapeutic anticoagulation group than in the prophylactic anticoagulation group (15 days [IQR 6–16] vs. 0 days [IQR 0–11]; $P = 0.028$). There was no between-group difference in in-hospital or 28-day mortality. Two patients treated with therapeutic anticoagulation had minor bleeding, and two patients in each group experienced thrombosis.[19] Additional evidence from large, multicenter trials is needed, and the trial results are expected soon.

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

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

Monitoring Coagulation Markers in Patients With COVID-19

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

Managing Antithrombotic Therapy in Patients With COVID-19

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

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

Chronic Anticoagulant or Antiplatelet Therapy

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

Patients with COVID-19 Who Are Managed as Outpatients

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

Hospitalized Patients With COVID-19

- For hospitalized patients with COVID-19, prophylactic dose anticoagulation should be prescribed unless contraindicated (e.g., a patient has active hemorrhage or severe thrombocytopenia) **(AIII)**. Although data supporting this recommendation are limited, a retrospective study showed reduced mortality in patients who received prophylactic anticoagulation, particularly if the patient had a sepsis-induced coagulopathy score ≥4.[4] For those without COVID-19, anticoagulant or antiplatelet therapy should not be used to prevent arterial thrombosis outside of the standard of care **(AIII)**. Anticoagulation is routinely used to prevent arterial thromboembolism in patients with heart arrhythmias. Although there are reports of strokes and myocardial infarction in patients with COVID-19, the incidence of these events is unknown.
- When imaging is not possible, patients with COVID-19 who experience an incident thromboembolic event or who are highly suspected to have thromboembolic disease should be managed with therapeutic doses of anticoagulant therapy as per the standard of care for patients without COVID-19 **(AIII)**.
- There are currently insufficient data to recommend either for or against using therapeutic doses of antithrombotic or thrombolytic agents for COVID-19 in patients who are hospitalized. Although there is evidence that multi-organ failure is more likely in patients with sepsis if they develop coagulopathy,[29] there is no convincing evidence to show that any specific antithrombotic treatment will influence outcomes in those with or without COVID-19. Participation in randomized trials is encouraged (if trials are available).
- Patients with COVID-19 who require extracorporeal membrane oxygenation or continuous renal replacement therapy or who have thrombosis of catheters or extracorporeal filters should be

treated as per the standard institutional protocols for those without COVID-19 **(AIII)**.

Hospitalized Children With COVID-19

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

Patients With COVID-19 Who Are Discharged from the Hospital

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

Special Considerations During Pregnancy and Lactation

Because pregnancy is a hypercoagulable state, the risk of thromboembolism is greater in pregnant individuals than in nonpregnant individuals.[33] It is not yet known whether COVID-19 increases this risk. In several cohort studies of pregnant women with COVID-19 in the United States and Europe, VTE was not reported as a complication even among women with severe disease, although the receipt of prophylactic or therapeutic anticoagulation varied across the studies.[34-36] The American College of Obstetricians and Gynecologists (ACOG) advises that although there are no data for or against thromboprophylaxis in the setting of COVID-19 in pregnancy, VTE prophylaxis can reasonably be considered for pregnant women hospitalized with COVID-19, particularly for those who have severe disease.[37] If there are no contraindications to use, the Society of Maternal Fetal Medicine recommends prophylactic heparin or low molecular weight heparin in critically ill or mechanically ventilated pregnant patients.[38] Several professional societies, including the American Society of Hematology and ACOG, have guidelines that specifically address the management of VTE in the context of pregnancy.[39,40] If delivery is threatened, or if there are other risks for bleeding, the risk of bleeding may outweigh the potential benefit of VTE prophylaxis in pregnancy.

There are no data on the use of scoring systems to predict VTE risk in pregnant individuals. Additionally, during pregnancy, the D-dimer level may not be a reliable predictor of VTE because there is a physiologic increase of D-dimer levels throughout gestation.[41-43]

In general, the preferred anticoagulants during pregnancy are heparin compounds. Because of its reliability and ease of administration, low-molecular weight heparin is recommended rather than unfractionated heparin for the prevention and treatment of VTE in pregnancy.[40]

Direct-acting anticoagulants are not routinely used during pregnancy due to the lack of safety data in pregnant individuals.[39] The use of warfarin to prevent or treat VTE should be avoided in pregnant individuals, regardless of their COVID-19 status, and especially during the first trimester due to the concern for teratogenicity.

Specific recommendations for pregnant or lactating individuals with COVID-19 include:

- If antithrombotic therapy is prescribed during pregnancy prior to a diagnosis of COVID-19, this therapy should be continued **(AIII)**.
- For pregnant patients hospitalized for severe COVID-19, prophylactic dose anticoagulation is recommended if there are no contraindications to its use **(BIII)**.
- As for nonpregnant patients, VTE prophylaxis after hospital discharge **is not recommended** for pregnant patients **(AIII)**. Decisions to continue VTE prophylaxis in the pregnant or postpartum patient should be individualized, considering concomitant VTE risk factors.
- Anticoagulation therapy use during labor and delivery requires specialized care and planning. It should be managed in pregnant patients with COVID-19 in a similar way as in pregnant patients with other conditions that require anticoagulation in pregnancy **(AIII)**.
- Unfractionated heparin, low molecular weight heparin, and warfarin do not accumulate in breast milk and do not induce an anticoagulant effect in the newborn; therefore, they can be used in breastfeeding women with or without COVID-19 who require VTE prophylaxis or treatment **(AIII)**. In contrast, direct-acting oral anticoagulants are not routinely recommended due to lack of safety data **(AIII)**.[39]

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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 shock[10] without an effect on clinical outcomes. Two other trials found no differences in any physiologic or outcome measure between the treatment and placebo groups.[11,12]

See *ClinicalTrials.gov* for a list of clinical trials that are evaluating the use of vitamin C in patients with COVID-19.

Other Considerations

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

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Vitamin D

Last Updated: July 17, 2020

Recommendation

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

General Information

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

Vitamin D deficiency (defined as a serum concentration of 25-hydroxyvitamin D ≤20 ng/mL) is common in the United States, particularly among persons of Hispanic ethnicity and Black race. These groups are overrepresented among cases of COVID-19 in the United States.[2] Vitamin D deficiency is also more common in older patients and patients with obesity and hypertension; these factors have been associated with worse outcomes in patients with C8OVID-19. In observational studies, low vitamin D levels have been associated with an increased risk of community-acquired pneumonia in older adults[3] and children.[4]

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

Vitamin D and COVID-19

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

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

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Zinc Supplementation and COVID-19

Last Updated: July 17, 2020

Recommendations

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

Rationale

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

Zinc supplementation alone or in combination with hydroxychloroquine for prevention and treatment of COVID-19 is currently being evaluated in clinical trials. The optimal dose of zinc for the treatment of COVID-19 is not established. The recommended dietary allowance for elemental zinc is 11 mg daily for men and 8 mg for nonpregnant women.[5] The doses used in registered clinical trials for COVID-19 vary between studies, with a maximum dose of zinc sulfate 220 mg (50 mg of elemental zinc) twice daily.

Long-term zinc supplementation can cause copper deficiency with subsequent reversible hematologic defects (i.e., anemia, leukopenia) and potentially irreversible neurologic manifestations (i.e., myelopathy, paresthesia, ataxia, spasticity).[6,7] Zinc supplementation for a duration as short as 10 months has been associated with copper deficiency.[8] In addition, oral zinc can decrease the absorption of medications that bind with polyvalent cations.[5] Because zinc has not been shown to have clinical benefit and may be harmful, the Panel **recommends against** using zinc supplementation above the recommended dietary allowance for the prevention of COVID-19, except in a clinical trial **(BIII)**.

Clinical Data

Retrospective Study of Hydroxychloroquine and Azithromycin With or Without Zinc

This study has not been peer-reviewed.

A retrospective observational study compared zinc supplementation to no zinc supplementation in hospitalized patients with COVID-19 who received hydroxychloroquine and azithromycin from March 2 to April 5, 2020. On March 25, the institution's standard of care was updated to include supplementation with zinc sulfate 220 mg orally twice daily. Patients who received any other investigational therapies were excluded. Only patients who were discharged from the hospital, transferred to hospice, or died were included in the analysis. Outcome measures included duration of hospital stay, duration of mechanical ventilation, maximum oxygen flow rate, average oxygen flow rate, average FiO_2, maximum FiO_2, admission to the intensive care unit (ICU), duration of ICU stay, death or transfer to hospice, need for intubation, and discharge destination.[9]

Results

- A total of 932 patients were included in this analysis; 411 patients received zinc, and 521 did not.
- The two groups had similar demographic characteristics.
- Patients who received zinc had higher absolute lymphocyte count and lower troponin and procalcitonin levels at baseline than those who did not receive zinc.
- In univariate analysis, no differences were observed between the two groups in duration of hospital stay, duration of mechanical ventilation, maximum oxygen flow rate, average oxygen flow rate, or average FiO_2.
- In bivariate logistic regression analysis, zinc supplementation was associated with a decreased mortality rate or rate of transfer to hospice; however, the association with a decreased mortality rate was no longer significant when analysis was limited to patients who were treated in the ICU.

Limitations

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

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

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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)**.

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 hypothesized[1] 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 ACE2[1] 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]

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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 Considerations in Pregnancy in the Antiviral Therapy and Immune-Based Therapy sections of these Guidelines.

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

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 Considerations in Pregnancy in the Antiviral Therapy and Immune-Based Therapy sections of these 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]

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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 Antiviral Therapy and Immune-Based Therapy sections of these guidelines to review special considerations for use of these drugs in children and refer to Table 2 and Table 3b for dosing recommendations 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.

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Special Considerations in Adults and Children With Cancer

Last Updated: August 27, 2020

Summary Recommendations
• 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 Immune-Based Therapy Under Evaluation for 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 with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, 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 Immune-Based Therapy Under Evaluation for 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 CYP34A 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]

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Special Considerations in Solid Organ Transplant, Hematopoietic Stem Cell Transplant, and Cellular Therapy Candidates, Donors, and Recipients

Last Updated: November 3, 2020

Summary Recommendations

Potential Transplant and Cellular Therapy Candidates
• 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)**.
Potential Transplant Donors
• 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)**.
  • 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)**.
  • 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)**.
Transplant and Cellular Therapy Recipients with COVID-19
• 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 Immune-Based Therapy 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)**.

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

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 Immune-Based Therapy 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]

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

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 2 and 3b for additional details.

Table 4. 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	• Hepatotoxicity (cholestatic hepatitis, rare) • Additive effect with other drugs that prolong the QTc interval.
Chloroquine and Hydroxychloroquine	• 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	• Moderate CYP3A4 inducer • Potential for additional immunosuppression and increased risk of OIs.
HIV Protease Inhibitors	• 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	• 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 3b.
Remdesivir	• Increase in levels of serum transaminases. • Accumulation of drug vehicle cyclodextrin in patients with kidney dysfunction.
Ribavirin	• Significant toxicities, including anemia, bradycardia, and an increase in serum transaminases levels.

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Special Considerations in People With Human Immunodeficiency Virus

Last Updated: October 9, 2020

Summary Recommendations

Prevention and Diagnosis of COVID-19

- 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)**.

Management of COVID-19

- 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.

Management of HIV

- 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).

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

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/mm^3. Persons with HIV and CD4 count of ≥500 cells/mm^3 have similar cellular immune function to persons without HIV. In people with HIV, a CD4 count <200 cells/mm^3 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/mm^3), 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.

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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 **(AII)**.   • 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 with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, 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

(AII).[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.

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Appendix A, Table 1. COVID-19 Treatment Guidelines Panel Members

Last Updated: October 9, 2020

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Community Member	
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Joseph Francis, MD, MPH	Department of Veterans Affairs, Washington, DC
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Appendix A, Table 2. COVID-19 Treatment Guidelines Panel Financial Disclosure for Companies Related to COVID-19 Treatment or Diagnostics

Last Updated: October 9, 2020

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
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Timothy Burgess, MD	None	N/A
Danielle M. Campbell, MPH	ViiV Healthcare	Summit Attendee
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Ann C. Collier, 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
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Laurie K. Doepel, BA	None	N/A
Amy L. Dzierba, PharmD	None	N/A
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Laura Evans, MD, MSc	None	N/A

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David V. Glidden, PhD	Gilead Sciences	Consultant
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Birgit Grund, PhD	None	N/A
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Alison Han, MD	None	N/A
Erica J. Hardy, MD, MMSc	None	N/A
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	Aurinia Pharmaceuticals	Advisory Board, Stockholder
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Arthur Kim, MD	None	N/A
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Jeffrey L. Lennox, MD	None	N/A
Andrea M. Lerner, MD, MS	None	N/A
Mitchell M. Levy, MD	Inotrem	Research Support
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	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
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Andrew T. Pavia, MD	GlaxoSmithKline	Consultant (related to influenza)
Nitin Seam, MD	None	N/A
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Steven Q. Simpson, MD	None	N/A
Kanal Singh, MD, MPH	None	N/A
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Pablo Tebas, MD	Inovio Pharmaceuticals	Research Support
Phyllis Tien, MD, MSc	Merck & Co.	Research Support
Timothy M. Uyeki, MD, MPH	None	N/A

Panel Member	Financial Disclosure	
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	Ansun BioPharma	Research Support
	Kyorin Pharmaceutical Co.	Advisory Board
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Kevin C. Wilson, MD	None	N/A
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	Eli Lilly and Company	Consultant
	Pfizer	Consultant