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: February 11, 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:

February 11, 2021

Key Updates to the Guidelines

Introduction

Each recommendation in the Guidelines is assigned a rating for the strength of the recommendation statement and the quality of the evidence that supports the recommendation. The rating scheme for the quality of evidence has been revised to better define the type of scientific evidence used to support the Panel's recommendations. The new ratings are as follows:

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 without major limitations **IIa:** Other randomized trials or subgroup analyses of randomized trials **IIb:** Nonrandomized trials or observational cohort studies **III:** Expert opinion

Prevention and Prophylaxis of SARS-CoV-2 Infection

A brief discussion of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccines that are currently available through Emergency Use Authorizations (EUAs) from the Food and Drug Administration (FDA) has been added to this section. This section also includes updated clinical trial data on the use of hydroxychloroquine for post-exposure prophylaxis (PEP).

Therapeutic Management of Patients With COVID-19

This section has been updated to add rationale to support the recommendations presented in Figure 1. Pharmacologic Management of Patients with COVID-19 Based on Disease Severity. Minor clarifying updates have also been made to the text in Figure 1.

Ivermectin

This section now incorporates the new information and recommendations from the Panel's statement on ivermectin that was released on January 14, 2021. A new table summarizes the results from several randomized clinical trials and retrospective cohort studies of ivermectin use in patients with COVID-19

that have been published in peer-reviewed journals or have been made available as manuscripts ahead of peer review.

Anti-SARS-CoV-2 Monoclonal Antibodies

Bamlanivimab and the combination of casirivimab and imdevimab are available through FDA EUAs for the treatment of outpatients with mild to moderate COVID-19 who are at high risk for progressing to severe disease and/or hospitalization. This new section of the Guidelines expands on the bamlanivimab statement that was released on November 18, 2020, and the casirivimab plus imdevimab statement that was released on December 2, 2020. This section also includes considerations for using these anti-SARS-CoV-2 monoclonal antibodies in pregnant people and children. A separate table has been created to summarize the clinical trial data that led to the issuance of the EUAs.

On February 9, 2021, the FDA issued an EUA for bamlanivimab plus etesevimab for the treatment of mild to moderate COVID-19 in outpatients who have received positive results on a nucleic acid amplification test or an antigen test for SARS-CoV-2 and who are at high risk for clinical progression. The Panel will issue recommendations on the use of bamlanivimab plus etesevimab shortly.

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

The information and recommendations from the Panel's December 14, 2020, statement on the use of baricitinib have been added to this section. The section also includes a more detailed description of the clinical data from the Adaptive COVID-19 Treatment Trial 2 (ACTT-2) study that led to the FDA issuing an EUA for the use of baricitinib and remdesivir for the treatment of certain hospitalized patients with COVID-19.

Other Updates to the Guidelines

The following sections received minor updates during this revision:

- General Considerations
- Testing for SARS-CoV-2 Infection
- Antithrombotic Therapy in Patients With COVID-19
- Zinc Supplementation and COVID-19

February 3, 2021

The COVID-19 Treatment Guidelines Panel's Statement on the Use of Tocilizumab (and Other Interleukin-6 Inhibitors) for the Treatment of COVID-19

Results from several randomized controlled trials of tocilizumab have been published since the last revision of the Interleukin-6 Inhibitors section of the Guidelines. In addition, preliminary results from the Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) have been released in a non-peer reviewed report. REMAP-CAP is the largest trial to date that has investigated the use of interleukin (IL)-6 inhibitors in patients with COVID-19. After reviewing the collective evidence from REMAP-CAP and other trials, the Panel has revised the recommendations on the use of tocilizumab and sarilumab in patients with COVID-19:

- For patients who are within 24 hours of admission to the intensive care unit (ICU) and require invasive or noninvasive mechanical ventilation or high-flow oxygen (>0.4 FiO_2/30 L/min oxygen flow), there are insufficient data to recommend either for or against the use of tocilizumab or sarilumab for the treatment of COVID-19.

    - Although many trials of tocilizumab for the treatment of COVID-19 have included patients who meet the above criteria, the collective data available to date preclude a definitive recommendation for or against the use of the drug.
    - In view of the results from the REMAP-CAP trial, some Panel members would administer a single dose of tocilizumab (8 mg/kg of actual body weight, up to 800 mg) in addition to dexamethasone to patients who meet the above criteria and who are also exhibiting rapid progression of respiratory failure.
    - Too few patients in REMAP-CAP received sarilumab for the Panel to assess its efficacy in the treatment of patients who met the above criteria.

- For patients who do not require ICU-level care or are admitted to the ICU but do not meet the above criteria, the Panel **recommends against** the use of **tocilizumab** or **sarilumab** for the treatment of COVID-19, except in a clinical trial **(BIIa)**.

Additional results of randomized controlled trials of tocilizumab and sarilumab will further understanding of the role these IL-6 inhibitors play in the treatment of COVID-19. Future updates to the Interleukin-6 Inhibitors section will include discussion of these studies.

The COVID-19 Treatment Guidelines Panel's Statement on the Use of Tocilizumab (and Other Interleukin-6 Inhibitors) for the Treatment of COVID-19

Last Updated: February 3, 2021

Background

Tocilizumab is a recombinant humanized anti-interleukin (IL)-6 receptor monoclonal antibody that is approved by the Food and Drug Administration (FDA) for the treatment of certain rheumatologic disorders and cytokine release syndrome induced by chimeric antigen receptor T cell (CAR-T) therapy. Similar agents in this class include sarilumab, which is FDA-approved for the treatment of rheumatoid arthritis. It is hypothesized that modulating the levels of pro-inflammatory IL-6 or its effects may improve the course of COVID-19. To date, no IL-6 inhibitor is FDA-approved or authorized for the treatment of COVID-19.

Brief Summary of Evidence

Initial studies evaluating the use of IL-6 inhibitors for the treatment of COVID-19 produced conflicting results. Many trials evaluating tocilizumab were limited by low power, heterogenous study populations with varying degrees of disease severity, and/or low frequency of concomitant use of corticosteroids, which has become the standard of care for patients with severe or critical COVID-19.[1-3] These trials failed to demonstrate a reduction of mortality within 1 month of tocilizumab treatment. However, other trials found that tocilizumab treatment lowered the incidence or duration of intensive care unit (ICU) and hospital stays (A Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients With Severe COVID-19 Pneumonia [COVACTA])[4] or lowered the composite rate of mechanical ventilation or death (Evaluating Minority Patients With Actemra [EMPACTA]).[5] The Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) enrolled critically ill patients requiring respiratory support who were admitted to an ICU. Patients were randomized within 24 hours of ICU admission, and within a median of 1.2 days (IQR 0.8–2.8) of hospitalization. The preliminary report of the REMAP-CAP trial noted that, compared to placebo, the use of either tocilizumab or sarilumab reduced both mortality and time to ICU discharge, and increased the number of organ support-free days.[6] The recommendations of the COVID-19 Treatment Guidelines Panel (the Panel) for tocilizumab and sarilumab are based on the collective evidence from clinical trials that have reported results to date.

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

- For patients who are within 24 hours of admission to the ICU and who require invasive or noninvasive mechanical ventilation or high-flow oxygen (>0.4 FiO_2/30 L/min of oxygen flow), there are insufficient data to recommend either for or against the use of tocilizumab or sarilumab for the treatment of COVID-19.
  - Although many trials of tocilizumab for the treatment of COVID-19 have included patients who meet the above criteria, the collective data available to date preclude a definitive recommendation for or against the use of the drug.
  - In view of the results from the REMAP-CAP trial (described below), some Panel members would administer a single dose of tocilizumab (8 mg/kg of actual body weight, up to 800 mg) in addition to dexamethasone to patients who meet the above criteria and who are also exhibiting rapid progression of respiratory failure.

    - Too few patients in REMAP-CAP received sarilumab for the Panel to assess its efficacy in the treatment of patients who met the above criteria.

- For patients who do not require ICU-level care or who are admitted to the ICU but do not meet the above criteria, the Panel recommends against the use of **tocilizumab** or **sarilumab** for the treatment of COVID-19, except in a clinical trial **(BIIa)**.

Additional Considerations:

- Panel members who would administer a single dose of tocilizumab would give the drug in combination with a course of dexamethasone therapy because >80% of the patients enrolled in the REMAP-CAP trial also received corticosteroids, which is consistent with the current standard of care.
- Several trials allowed for a second dose of tocilizumab per discretion of the investigator. Currently, there are insufficient data to support repeated dosing of tocilizumab.
- There were very few immunocompromised patients enrolled in the REMAP-CAP trial; thus, the safety of using a combination of tocilizumab and dexamethasone for these patients is unknown. The risk of superinfection should be considered and monitored for, particularly in the setting of concomitant corticosteroid use.
- There are no data from systematic observational cohorts or randomized controlled trials on the use of IL-6 inhibitors in children for the treatment of acute COVID-19. In children, tocilizumab has been used to treat cytokine release syndrome associated with CAR-T therapy and systemic and polyarticular juvenile idiopathic arthritis.
- Use of tocilizumab for the treatment of COVID-19 may affect supplies for other indications, such as rheumatic diseases and cytokine release syndrome related to CAR-T therapy. Health systems are encouraged to ensure an adequate supply of tocilizumab for patients who need the drug for the FDA-approved indications.
- The collective evidence that led to the Panel's recommendations are based on studies using tocilizumab. The results of randomized controlled trials of sarilumab that are underway will further understanding of the role sarilumab plays in the treatment of COVID-19.
- Sarilumab and tocilizumab have a similar mechanism of action. However, in the REMAP-CAP trial, the number of participants who received sarilumab was relatively small. Moreover, the trial evaluated sarilumab for intravenous administration, which is not the approved formulation in the United States.

Clinical Trial Data

Critically Ill Patients Who Were Admitted to an Intensive Care Unit

This study has not been peer reviewed.

To date, the largest trial that has investigated the use of IL-6 inhibitors in patients with COVID-19 is the REMAP-CAP trial, a multinational, adaptive, randomized controlled trial that randomly assigned 803 participants with suspected or confirmed COVID-19 to receive immune modulation with an IL-6 receptor antagonist (353 participants received tocilizumab and 48 received sarilumab) or the standard of care (402 participants).[6] In a preliminary non-peer reviewed report of outcomes among critically ill patients who were hospitalized for <15 days, and were admitted to an ICU for <24 hours, and required respiratory and/or cardiovascular organ support, the following treatment effects were described:

- Compared to standard of care, one or two doses of tocilizumab decreased in-hospital mortality

(28% of the tocilizumab patients vs. 36% of the standard of care patients died), improved in-hospital survival (aOR 1.64; 95% credible intervals [CrI], 1.14–2.35), and increased the number of organ support-free days (aOR 1.64; 95% CrI, 1.25–2.14).

- Compared to standard of care, one dose of sarilumab (n = 48) decreased in-hospital mortality (22% of the sarilumab patients vs. 36% of the standard of care patients died), improved in-hospital survival (aOR 2.01; 95% CrI, 1.18–4.71), and increased the number of organ support-free days (aOR 1.76; 95% CrI, 1.17–2.91).

The distribution of patients who required respiratory support at baseline included 28.8% requiring high-flow oxygen, 41.5% requiring noninvasive mechanical ventilation, and 29.4% requiring invasive mechanical ventilation. More than 80% of the patients received concomitant corticosteroids. More than 75% of the participants received the IL-6 inhibitors within 3 days of hospital admission, suggesting that the benefit of tocilizumab or sarilumab may occur primarily among patients whose condition is rapidly deteriorating. An assessment of the safety of tocilizumab or sarilumab is limited by the low number of adverse events reported in this trial.

Several other large, well-conducted, randomized controlled trials that included critically ill patients reported mixed results. The reasons for the differences across the trials is uncertain. Possibilities include the varying degree of respiratory dysfunction among the patients enrolled in each study, racial and ethnic differences in the populations studied, differences in the frequency of corticosteroid use (with higher use in the REMAP-CAP and EMPACTA trials), and differences in the use of other co-interventions because the trials were conducted at different times during the pandemic as COVID-19 treatment practice evolved.

Severely Ill Patients Who Require Supplemental Oxygen but Not High-Flow Oxygen, Invasive Mechanical Ventilation, or Admission to an Intensive Care Unit

The EMPACTA trial randomized patients with severe COVID-19 (n = 389) to tocilizumab or placebo; those who required noninvasive or invasive mechanical ventilation were subsequently excluded from the trial.[5] More than 80% of the participants in the modified intention-to-treat population (n = 377) were members of a racial or ethnic minority group.[5] The primary outcome, a composite of mortality or invasive mechanical ventilation at Day 28, favored tocilizumab over placebo (12.0% in the tocilizumab arm vs. 19.3% in the placebo arm; HR 0.56; 95% CI, 0.33–0.97; $P = 0.04$). However, there was no difference between the arms in all-cause mortality at Day 28.

The COVACTA trial enrolled 452 patients with COVID-19; 69% of the participants required noninvasive or invasive mechanical ventilation.[4] The participants were randomized 2:1 to tocilizumab or placebo. There was no difference between the arms in the primary outcome, clinical status (based on a seven-point ordinal scale) at Day 28 (OR 1.19; 95% CI, 0.81–1.76), or overall mortality. However, results for secondary outcome measures indicated that patients who received tocilizumab had a shorter time to hospital discharge than those who received placebo (20 days in the tocilizumab arm vs. 28 days in the placebo arm; HR 1.35; 95% CI, 1.02–1.79; $P = 0.04$) and a shorter ICU stay (9.8 days in the tocilizumab arm vs. 15.5 days in the placebo arm; $P = 0.05$).

The randomized, controlled, Boston Area COVID-19 Consortium (BACC) Bay Tocilizumab Trial enrolled 243 patients and found no effect on the primary outcome measure, a composite of time to intubation or death at 28 days (HR 0.83; 95% CI, 0.38–1.81; $P = 0.64$).[1] Similarly, the open-label, international CORIMUNO-19–Tocilizumab (CORIMUNO-TOCI-1)[2] and Efficacy of Early Administration of Tocilizumab in COVID-19 Patients (RCT-TCZ-COVID-19)[7] trials did not identify a mortality benefit from tocilizumab in patients with moderate or severe COVID-19 who did not require organ support. These latter trials each had significant methodological limitations, including lack of

blinding, insufficient power, and/or lack of a racially and ethnically diverse cohort.

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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Introduction

Last Updated: February 11, 2021

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

Panel Composition

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

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

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

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

Development of the Guidelines

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

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

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

Method of Synthesizing Data and Formulating Recommendations

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

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

Table 1. Recommendation Rating Scheme

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

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

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

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

clinical trials are needed to further define the role of the intervention.

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

Evolving Knowledge on Treatment for COVID-19

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

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

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

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

Overview of COVID-19

Last Updated: December 17, 2020

Epidemiology

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

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

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

Clinical Presentation

The estimated incubation period for COVID-19 is up to 14 days from the time of exposure, with a median incubation period of 4 to 5 days.[6,18,19] The spectrum of illness can range from asymptomatic infection to severe pneumonia with acute respiratory distress syndrome (ARDS) and death. Among 72,314 persons with COVID-19 in China, 81% of cases were reported to be mild (defined in this study as no pneumonia or mild pneumonia), 14% were severe (defined as dyspnea, respiratory frequency ≥30 breaths/min, saturation of oxygen [SpO_2] ≤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: February 11, 2021

Summary Recommendations

• To diagnose acute infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the COVID-19 Treatment Guidelines Panel (the Panel) recommends using a nucleic acid amplification test (NAAT) with a sample collected from the upper respiratory tract (i.e., nasopharyngeal, nasal, or oropharyngeal specimen) **(AIII)**.
• For intubated and mechanically ventilated adults who are suspected to have COVID-19 but who do not have a confirmed diagnosis:
  • The Panel recommends obtaining lower respiratory tract samples to establish a diagnosis of COVID-19 if an initial upper respiratory tract sample is negative **(BII)**.
  • The Panel recommends obtaining endotracheal aspirates over bronchial wash or bronchoalveolar lavage samples when collecting lower respiratory tract samples to establish a diagnosis of COVID-19 **(BII)**.
• In asymptomatic persons, a NAAT should not be repeated within 90 days of previous SARS-CoV-2 infection, even following a significant exposure to SARS-CoV-2 **(AIII)**.
• Because of reports of SARS-CoV-2 reinfection after an initial diagnosis of infection, a NAAT should be considered for persons who have recovered from previous infection and present with symptoms compatible with SARS-CoV-2 infection, in the absence of an alternative diagnosis **(BIII)**.
• The Panel **recommends against** the use of serologic (i.e., antibody) testing as the sole basis for diagnosis of acute SARS-CoV-2 infection **(AIII)**.
• The Panel **recommends against** the use of serologic (i.e., antibody) testing to determine whether a person is immune to SARS-CoV-2 infection (see below for details) **(AIII)**.

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

Diagnostic Testing for SARS-CoV-2 Infection

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

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

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

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

Nucleic Acid Amplification Testing for SARS-CoV-2 Infection

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

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

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

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

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

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

Antigen Testing for SARS-CoV-2 Infection

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

Increasingly, data are available to guide the use of antigen tests as screening tests to detect or exclude SARS-CoV-2 infection in asymptomatic persons, or to determine whether a person who was previously confirmed to have SARS-CoV-2 infection is still infectious. CDC has developed an antigen testing algorithm for persons who have symptoms of COVID-19, persons who are asymptomatic and have a close contact with COVID-19, and persons who are asymptomatic and have no known exposure to a person with COVID-19.[18]

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

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

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

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

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

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

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

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

Serologic Testing and Immunity to SARS-CoV-2 Infection

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

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

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

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

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

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

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

- Make decisions about how to group persons in congregate settings (e.g., schools, dormitories, correctional facilities)
- Determine whether persons may return to the workplace
- Assess for prior infection solely to determine whether to vaccinate an individual
- Assess for immunity to SARS-CoV-2 following vaccination, except in clinical trials

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Prevention and Prophylaxis of SARS-CoV-2 Infection

Last Updated: February 11, 2021

Summary Recommendations
• The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of any drugs for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pre-exposure prophylaxis (PrEP), except in a clinical trial **(AIII)**. • The Panel **recommends against** the use of **hydroxychloroquine** for SARS-CoV-2 post-exposure prophylaxis (PEP) **(AI)**. • The Panel **recommends against** the use of other drugs for SARS-CoV-2 PEP, except in a clinical trial **(AIII)**. • The Panel recommends that health care providers follow recommendations from the Advisory Committee on Immunization Practices when using SARS-CoV-2 vaccines **(AI)**..
Rating of Recommendations: A = Strong; B = Moderate; C = Optional **Rating of Evidence:** I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

General Prevention Measures

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

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

Vaccines

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

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

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

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

Pre-Exposure Prophylaxis

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

Rationale

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

Clinical Trial Data

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

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

Study Population

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

Results

- The study was based on the assumption of a 10% infection rate for the planned inclusion of 100 participants per arm.
- Between April 9 and July 14, 2020, community infection rates declined. At the time of the second

interim analysis (when 125 of 132 participants who provided consent were evaluable for the primary endpoint), the Data Safety Monitoring Board recommended early termination of the study for futility.

- Four participants in each group developed SARS-CoV-2 infection (positivity rate of 6.3% vs. 6.6% in the hydroxychloroquine and placebo groups, respectively; $P > 0.99$). Across the groups, six individuals developed symptoms of COVID-19, but none required hospitalization.
- Serologic testing for anti-spike protein immunoglobulin (Ig) M, IgG, and nucleocapsid protein IgG demonstrated more positive results among participants in the hydroxychloroquine group (four participants [7.4%]) than in the placebo group (two participants [3.7%]), although the difference was not statistically significant ($P = 0.40$).
- Mild adverse events were more common among participants in the hydroxychloroquine group than in the placebo group (45% vs. 26%; $P = 0.04$). The greatest difference was the increased frequency of mild diarrhea in the hydroxychloroquine group.
- The rates of treatment discontinuation were similar in the hydroxychloroquine group (19%) and the placebo group (16%).
- There were no cardiac events in either arm and no significant difference in the median frequency of changes in QTc between the study arms ($P = 0.98$).

Limitations

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

Interpretation

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

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

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

Study Population

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

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

Results

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

Limitations

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

Interpretation

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

Post-Exposure Prophylaxis

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

Rationale

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

Clinical Trial Data

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

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

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

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

Study Population

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

Results

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

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

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

Limitations

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

Interpretation

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

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

This randomized, double-blind, controlled trial included 821 participants who self-enrolled in the study using an internet-based survey. Participants were randomized to receive either hydroxychloroquine 800 mg given once, followed by hydroxychloroquine 600 mg given 6 to 8 hours later, and then hydroxychloroquine 600 mg given once daily for 4 additional days or placebo. Because enrollment was done online, study drugs were sent by overnight mail, resulting in more than 50% of participants initiating the first dose of their assigned treatment 3 to 4 days after exposure to SARS-CoV-2.[15]

Study Population

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

Results

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

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

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

Limitations

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

Interpretation

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

Cluster-Randomized Trial of High-Risk Exposures in Spain

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

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

Study Population

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

Results

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

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

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

Limitations

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

Interpretation

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

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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) **(AIIa)**.
- For health care workers who are performing non-aerosol-generating procedures on patients with COVID-19 who are on closed-circuit mechanical ventilation, the Panel recommends using an N95 respirator (or equivalent or higher-level respirator) in addition to other PPE (i.e., gloves, gown, and eye protection such as a face shield or safety goggles) because ventilator circuits may become disrupted unexpectedly **(BIII)**.
- The Panel recommends that endotracheal intubation in patients with COVID-19 be performed by health care providers with extensive airway management experience, if possible **(AIII)**.
- The Panel recommends that intubation be performed using video laryngoscopy, if possible **(CIIa)**.

Hemodynamics

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

Oxygenation and Ventilation

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

improve oxygenation **(CIIa)**.

- The Panel **recommends against** using awake prone positioning as a rescue therapy for refractory hypoxemia to avoid intubation in patients who otherwise meet the indications for intubation and mechanical ventilation **(AIII)**.
- If intubation becomes necessary, the procedure should be performed by an experienced practitioner in a controlled setting due to the enhanced risk of severe acute respiratory syndrome coronavirus 2 exposure to health care practitioners during intubation **(AIII)**.
- For mechanically ventilated adults with COVID-19 and acute respiratory distress syndrome (ARDS):
  - The Panel recommends using low tidal volume (VT) ventilation (VT 4–8 mL/kg of predicted body weight) over higher VT ventilation (VT >8 mL/kg) **(AIIa)**.
  - The Panel recommends targeting plateau pressures of <30 cm H_2O **(AIIa)**.
  - The Panel recommends using a conservative fluid strategy over a liberal fluid strategy **(BIIa)**.
  - The Panel **recommends against** the routine use of inhaled nitric oxide **(AIIa)**.
- For mechanically ventilated adults with COVID-19 and moderate-to-severe ARDS:
  - The Panel recommends using a higher positive end-expiratory pressure (PEEP) strategy over a lower PEEP strategy **(BIIa)**.
  - For mechanically ventilated adults with COVID-19 and refractory hypoxemia despite optimized ventilation, the Panel recommends prone ventilation for 12 to 16 hours per day over no prone ventilation **(BIIa)**.
- For mechanically ventilated adults with COVID-19 and moderate-to-severe ARDS:
  - The Panel recommends using, as needed, intermittent boluses of neuromuscular blocking agents (NMBA) or continuous NMBA infusion to facilitate protective lung ventilation **(BIIa)**.
  - In the event of persistent patient-ventilator dyssynchrony, or in cases where a patient requires ongoing deep sedation, prone ventilation, or persistently high plateau pressures, the Panel recommends using a continuous NMBA infusion for up to 48 hours as long as patient anxiety and pain can be adequately monitored and controlled **(BIII)**.
- For mechanically ventilated adults with COVID-19, severe ARDS, and hypoxemia despite optimized ventilation and other rescue strategies:
  - The Panel recommends using recruitment maneuvers rather than not using recruitment maneuvers **(CIIa)**.
  - If recruitment maneuvers are used, the Panel **recommends against** using staircase (incremental PEEP) recruitment maneuvers **(AIIa)**.
  - The Panel recommends using an inhaled pulmonary vasodilator as a rescue therapy; if no rapid improvement in oxygenation is observed, the treatment should be tapered off **(CIII)**.

Acute Kidney Injury and Renal Replacement Therapy

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

Pharmacologic Interventions

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

Extracorporeal Membrane Oxygenation

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

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

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

General Considerations

Last Updated: February 11, 2021

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

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

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

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

Comorbid Conditions

Certain attributes and comorbidities (e.g., older age, cardiovascular disease, diabetes, chronic obstructive pulmonary disease, cancer, renal disease, obesity, sickle cell disease, receipt of a solid organ transplant) are associated with an increased risk of severe illness from COVID-19.[2]

Bacterial Superinfection of COVID-19-Associated Pneumonia

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

Inflammatory Response Due to COVID-19

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

Patients with COVID-19 and severe pulmonary involvement are well described to also manifest extrapulmonary disease and to exhibit laboratory markers of acute inflammation. Patients with these

manifestations of severe pulmonary disease typically progress to critical illness 10 to 12 days after the onset of COVID-19 symptoms.

Multisystem Inflammatory Syndrome in Adults

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

MIS-A is defined by the following criteria:

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

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

COVID-19-Induced Cardiac Dysfunction, Including Myocarditis

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

Thromboembolic Events and COVID-19

Critically ill patients with COVID-19 have been observed to have a prothrombotic state, which is characterized by the elevation of certain biomarkers, and there is an apparent increase in the incidence of venous thromboembolic disease in this population. In some studies, thromboemboli have been diagnosed in patients who received chemical prophylaxis with heparinoids.[17-19] Autopsy studies provide additional evidence of both thromboembolic disease and microvascular thrombosis in patients with COVID-19.[20] Some authors have called for routine surveillance of ICU patients for venous thromboembolism.[21] See the Antithrombotic Therapy in Patients with COVID-19 section for a more detailed discussion.

Renal and Hepatic Dysfunction Due to COVID-19

Although SARS-CoV-2 is primarily a pulmonary pathogen, renal and hepatic dysfunction are consistently described in patients with severe COVID-19.[4] In one case series of patients with critical

disease, >15% of the patients required continuous renal replacement therapy.[6] See the Acute Kidney Injury and Renal Replacement Therapy section for a more detailed discussion.

Considerations in Children

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

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

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

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

Sedation Management in Patients With COVID-19

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

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

A. Assess, prevent, and manage pain;

B. Both spontaneous awakening and breathing trials;

C. Choice of analgesia and sedation;

D. Delirium: assess, prevent, and manage;

E. Early mobility and exercise; *and*

F. Family engagement and empowerment.

The A-F Bundle also provides frontline staff with practical application strategies for each element.[34] The A-F Bundle should be incorporated using an interprofessional team model. This approach helps standardize communication among team members, improves survival, and reduces long-term cognitive dysfunction of patients.[35] Despite the known benefits of the A-F Bundle, its impact has not been directly assessed in patients with COVID-19; however, the use of the Bundle should be encouraged, when appropriate, to improve ICU patient outcomes. Prolonged mechanical ventilation of COVID-19 patients, coupled with deep sedation and potentially neuromuscular blockade, increases the workload of ICU

staff. Additionally, significant drug shortages may force clinicians to use older sedatives with prolonged durations of action and active metabolites, impeding routine implementation of the PADIS Guidelines. This puts patients at additional risk for ICU and post-ICU complications.

Post-Intensive Care Syndrome

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

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

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

Other Intensive Care Unit-Related Complications

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

Advance Care Planning and Goals of Care

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

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

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

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

or safety goggles) **(AIIa)**.

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

Rationale

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

Recommendations

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

Rationale

Practices that maximize the chances of first-pass success and minimize aerosolization should be used when intubating patients with suspected or confirmed COVID-19.[10,11] Thus, the Panel recommends that the health care worker with the most experience and skill in airway management be the first to attempt intubation. The close facial proximity of direct laryngoscopy can expose health care providers to higher concentrations of viral aerosols. It is also important to avoid having unnecessary staff in the room during intubation procedures.

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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 **(BIIa)**.

Rationale

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

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

Recommendation

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

Rationale

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

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

Recommendation

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

Rationale

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

Additional Recommendations Based on General Principles of Critical Care

- The Panel **recommends against** using hydroxyethyl starches for intravascular volume replacement in patients with sepsis or septic shock **(AIIa)**.
- The Panel recommends norepinephrine as the first-choice vasopressor **(AIIa)**. The Panel recommends adding either vasopressin (up to 0.03 units/min) **(BIIa)** or epinephrine **(CIIb)** to norepinephrine to raise mean arterial pressure to target or adding vasopressin (up to 0.03 units/minute) **(CIIa)** to decrease norepinephrine dosage.
- When norepinephrine is available, the Panel **recommends against** using dopamine for patients with COVID-19 and shock **(AIIa)**.
- The Panel **recommends against** using low-dose dopamine for renal protection **(BIIa)**.
- The Panel recommends using dobutamine in patients who show evidence of cardiac dysfunction and persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents **(BIII)**.
- The Panel recommends that all patients who require vasopressors have an arterial catheter placed as soon as practical, if resources are available **(BIII)**.
- For adults with COVID-19 and refractory septic shock who are not receiving corticosteroids to treat their COVID-19, the Panel recommends using low-dose corticosteroid therapy ("shock-reversal") over no corticosteroid therapy **(BIIa)**.
- 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) **(BIIa)**.
- In the absence of an indication for endotracheal intubation, the Panel recommends a closely monitored trial of NIPPV for adults with COVID-19 and acute hypoxemic respiratory failure and for whom HFNC is not available **(BIIa)**.
- For patients with persistent hypoxemia despite increasing supplemental oxygen requirements in whom endotracheal intubation is not otherwise indicated, the Panel recommends considering a trial of awake prone positioning to improve oxygenation **(CIIa)**.
- The Panel **recommends against** using awake prone positioning as a rescue therapy for refractory hypoxemia to avoid intubation in patients who otherwise meet the indications for intubation and mechanical ventilation **(AIII)**.
- If intubation becomes necessary, the procedure should be performed by an experienced practitioner in a controlled setting due to the enhanced risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exposure to health care practitioners during intubation **(AIII)**.

Rationale

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

Goal of Oxygenation

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

Regarding the potential harm of maintaining an SpO_2 <92%, a trial randomly assigned ARDS patients without COVID-19 to either a conservative oxygen strategy (target SpO_2 of 88% to 92%) or a liberal oxygen strategy (target SpO_2 ≥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) **(AIIa)**.
- The Panel recommends targeting plateau pressures of <30 cm H_2O **(AIIa)**.
- The Panel recommends using a conservative fluid strategy over a liberal fluid strategy **(BIIa)**.
- The Panel **recommends against** the routine use of inhaled nitric oxide **(AIIa)**.

Rationale

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

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

Recommendations

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

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

Rationale

PEEP is beneficial in patients with ARDS because it prevents alveolar collapse, improves oxygenation, and minimizes atelectotrauma, a source of ventilator-induced lung injury. A meta-analysis of individual patient data from the three largest trials that compared lower and higher levels of PEEP in patients without COVID-19 found lower rates of ICU mortality and in-hospital mortality with higher PEEP in those with moderate (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 **(BIIa)**.
- In the event of persistent patient-ventilator dyssynchrony, or in cases where a patient requires ongoing deep sedation, prone ventilation, or persistently high plateau pressures, the Panel recommends using a continuous NMBA infusion for up to 48 hours as long as patient anxiety and pain can be adequately monitored and controlled **(BIII)**.

Rationale

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

Rescue Therapies for Mechanically Ventilated Adults With Acute Respiratory Distress Syndrome

Recommendations

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

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

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

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 Immunomodulators Under Evaluation for the Treatment of COVID-19.

Corticosteroids

See Therapeutic Management of Patients with COVID-19 for recommendations on the use of dexamethasone with or without remdesivir.

Adjunctive Therapy

Recommendations 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: February 11, 2021

Executive Summary

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

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

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

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

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

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

Doses and durations are listed in the footnote.

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS
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] The Panel recommends against the use of **dexamethasone** or **other corticosteroids (AIII)**.[b]
Hospitalized but Does Not Require Supplemental Oxygen	The Panel recommends against the use of **dexamethasone (AIIa)** or **other corticosteroids (AIII).**[b] 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 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**[c,d] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone**[e] **plus remdesivir**[c,d] (e.g., for patients who require increasing amounts of supplemental oxygen) **(BIII)**[f,g] • **Dexamethasone**[e] (e.g., when combination therapy with remdesivir cannot be used or is not available) **(BI)**
Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	Use one of the following options: • **Dexamethasone**[e,g] **(AI)** • **Dexamethasone**[e] **plus remdesivir**[c,d] **(BIII)**[f,g]
Hospitalized and Requires Invasive Mechanical Ventilation or ECMO	**Dexamethasone**[e] **(AI)**[h]

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 Anti-SARS-CoV-2 Monoclonal Antibodies section for more information on using bamlanivimab and casirivimab plus imdevimab in patients with mild to moderate COVID-19.
[b] Patients who are receiving corticosteroids for other indications should continue therapy for their underlying conditions as directed by their health care providers.
[c] The remdesivir dose is 200 mg IV for one dose, followed by remdesivir 100 mg IV once daily for 4 days or until hospital discharge (unless the patient is in a health care setting that can provide acute care that is similar to inpatient hospital care). Treatment duration may be extended to up to 10 days if there is no substantial clinical improvement by Day 5.
[d] For patients who are receiving remdesivir but progress to requiring oxygen through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or ECMO, remdesivir should be continued until the treatment course is completed.
[e] The dexamethasone dose is 6 mg IV or PO once daily for 10 days or until hospital discharge. If dexamethasone is not available, equivalent doses of other corticosteroids (e.g., prednisone, methylprednisolone, hydrocortisone) may be used. See the Corticosteroids section for more information.
[f] The combination of dexamethasone and remdesivir has not been studied in clinical trials.
[g] In the rare circumstances where corticosteroids cannot be used, **baricitinib plus remdesivir** can be used **(BIIa)**. The FDA has issued an EUA for baricitinib use in combination with remdesivir. The dose for baricitinib is 4 mg PO once daily for 14 days or until hospital discharge.
[h] The combination of **dexamethasone and remdesivir** may be considered for patients who have recently been intubated **(CIII)**. The Panel **recommends against** the use of remdesivir monotherapy in these patients.

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

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

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

Recommendations

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

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

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

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

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

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

Rationale for Recommending Against the Use of Dexamethasone or Other Corticosteroids

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

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

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

Recommendations

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

Rationale for Recommending Against the Use of Dexamethasone or Other Corticosteroids

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

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

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

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

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

Selected Clinical Data for additional information.

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

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

Recommendations

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

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

Additional Considerations

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

Rationale for the Use of Remdesivir

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

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

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

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

Rationale for the Use of Remdesivir Plus Dexamethasone

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

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

Rationale for the Use of Dexamethasone

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

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

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

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

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

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

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

Recommendations

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

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

Additional Considerations

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

Rationale for the Use of Dexamethasone

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

Rationale for the Use of Remdesivir Plus Dexamethasone

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

Rationale for Not Recommending Remdesivir Monotherapy

In ACTT-1, there was no observed difference in time to recovery between the remdesivir and placebo groups (recovery rate ratio 1.09; 95% CI, 0.76–1.57) in the subgroup of participants who required high-flow oxygen or noninvasive ventilation at enrollment (n = 193). A post hoc analysis did not show a survival benefit for remdesivir at Day 29.[1] However, the trial was not powered to detect differences in outcomes within subgroups. The Panel **does not recommend** using **remdesivir monotherapy** in these patients because there is uncertainty regarding whether remdesivir alone confers a clinical benefit in this subgroup **(AIIa)**. Dexamethasone or remdesivir plus dexamethasone are better treatment options for COVID-19 in this group of patients.

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

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

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

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

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

Recommendations

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

Additional Considerations

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

Rationale for the Use of Dexamethasone Monotherapy

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

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

Considerations Related to the Use of Dexamethasone Plus Remdesivir Combination Therapy

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

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

Rationale for Recommending Against the Use of Remdesivir Monotherapy

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

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

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

Last Updated: February 11, 2021

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 2d. **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 **(AIIa)**. • The Panel **recommends against** the use of **high-dose chloroquine** (600 mg twice daily for 10 days) for the treatment of COVID-19 **(AI)**. **Lopinavir/Ritonavir and Other HIV Protease Inhibitors** • The Panel **recommends against** the use of **lopinavir/ritonavir** and **other HIV protease inhibitors** for the treatment of COVID-19 in hospitalized patients **(AI)**. • The Panel **recommends against** the use of **lopinavir/ritonavir** and **other HIV protease inhibitors** for the treatment of COVID-19 in nonhospitalized patients **(AIII)**. **Ivermectin** • There are insufficient data for the Panel to recommend either for or against the use of ivermectin for the treatment of COVID-19. Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of ivermectin in the treatment of COVID-19.
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

Antiviral Therapy

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

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

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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 Table 2a for more information.

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

Monitoring, Adverse Effects, and Drug-Drug Interactions

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

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

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

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

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

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

See Table 2d for more information.

Considerations in Pregnancy

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

Considerations in Children

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

Clinical Trials

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

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Table 2a. Remdesivir: Selected Clinical Data

Last Updated: February 11, 2021

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

Study Design	Methods	Results	Limitations and Interpretation
Adaptive COVID-19 Treatment Trial (ACTT-1)[1]			

Multinational, placebo-controlled, double-blind RCT in hospitalized patients (n = 1,062)	**Key Inclusion Criteria:**
	• Aged ≥18 years
	• Laboratory-confirmed SARS-CoV-2 infection
	• At least 1 of the following conditions:
	  • Pulmonary infiltrates, as determined by radiographic imaging
	  • SpO_2 ≤94% on room air
	  • Required supplemental oxygen
	  • Required mechanical ventilation
	  • Required ECMO
	Key Exclusion Criteria:
	• ALT or AST >5 times ULN
	• eGFR <30 mL/min
	• Pregnancy or breastfeeding
	Interventions:
	• IV RDV 200 mg on Day 1, then 100 mg daily for up to 9 more days
	• Placebo for 10 days
	Primary Endpoint:
	• Time to clinical recovery
	Ordinal Scale Definitions:
	1. Not hospitalized, no limitations
	2. Not hospitalized, with limitations
	3. Hospitalized, no active medical problems
		Number of Participants:
		• RDV (n = 541) and placebo (n = 521)
		Participant Characteristics:
		• Median time from symptom onset to randomization was 9 days (IQR 6–12 days).
		Outcomes
		Overall Results:
		• RDV reduced time to recovery compared to placebo (10 days vs. 15 days; RRR 1.29; 95% CI, 1.12–1.49; $P < 0.001$).
		• Clinical improvement based on ordinal scale was higher at Day 15 in RDV arm (OR 1.5; 95% CI, 1.2–1.9; $P < 0.001$).
		• No statistically significant difference in mortality by Day 29 between RDV and placebo arms (HR 0.73; 95% CI, 0.52–1.03; $P = 0.07$).
		• Benefit of RDV was greatest in patients randomized during the first 10 days after symptom onset.
		Results by Disease Severity at Enrollment:
		• No difference in median time to recovery between arms among patients who had mild to moderate disease at enrollment.
		• Benefit of RDV for reducing time to recovery was clearest in patients who required supplemental oxygenation at enrollment (n = 435; RRR 1.45; 95% CI, 1.18–1.79), and RDV appeared to confer
			Limitations:
			• Wide range of disease severity; study was not powered to detect differences within subgroups
			• Powered to detect differences in clinical improvement, not mortality
			• No data collected on longer-term morbidity
			Interpretation:
			• In patients with severe COVID-19, RDV reduced time to clinical recovery.
			• Benefit of RDV was most apparent in hospitalized patients on supplemental oxygen.
			• No observed benefit in those on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO, but the study was not powered to detect differences within subgroups.
			• No observed benefit of RDV in patients with mild or moderate COVID-19, but the number of participants in these categories was relatively small.

Study Design	Methods	Results	Limitations and Interpretation
Adaptive COVID-19 Treatment Trial (ACTT-1)[1], continued			
	4. Hospitalized, not on oxygen 5. Hospitalized, on oxygen 6. Hospitalized, on high-flow oxygen or noninvasive mechanical ventilation 7. Hospitalized, on mechanical ventilation or ECMO 8. Death	a survival benefit in this subgroup (HR for death by Day 29 0.30; 95% CI, 0.14–0.64). • No observed difference in time to recovery between arms in patients on high-flow oxygen or noninvasive ventilation at enrollment (RRR 1.09; 95% CI, 0.76–1.57). No evidence that RDV affected mortality rate in this subgroup (HR 1.02; 95% CI, 0.54–1.91). • No observed difference in time to recovery between arms in patients on mechanical ventilation or ECMO at enrollment (RRR 0.98; 95% CI, 0.70–1.36). No evidence that RDV affected mortality rate in this subgroup (HR 1.13; 95% CI, 0.67–1.89). *Safety Results:* • Percentages of patients with SAEs were similar between arms (25% vs. 32%). • Transaminase elevations: 6% of RDV recipients, 10.7% of placebo recipients	
Remdesivir Versus Placebo for Severe COVID-19 in China[2]			
Multicenter, placebo-controlled, double-blind RCT in hospitalized patients with severe COVID-19 (n = 237)	**Key Inclusion Criteria:** • Aged ≥18 years • Laboratory-confirmed SARS-CoV-2 infection • Time from symptom onset to randomization <12 days • SpO_2 ≤94% on room air or PaO_2/FiO_2 <300 mm Hg • Radiographically confirmed pneumonia **Key Exclusion Criteria:** • ALT or AST >5 times ULN • eGFR <30 mL/min • Pregnancy or breastfeeding	**Number of Participants:** • ITT analysis: RDV (n = 158) and placebo (n = 78) • Study stopped before reaching target enrollment of 453 patients due to control of the COVID-19 outbreak in China. **Participant Characteristics:** • Median time from symptom onset to randomization: 9 days for RDV arm, 10 days for placebo arm • Receipt of corticosteroids: 65% of patients in RDV arm, 68% in placebo arm • Receipt of LPV/RTV: 28% of patients in RDV arm, 29% in placebo arm	**Limitations:** • Sample size did not have sufficient power to detect differences in clinical outcomes. • Use of concomitant medications (i.e., corticosteroids, LPV/RTV, IFNs) may have obscured effects of RDV. **Interpretation:** • No difference in time to clinical improvement, 28-day mortality, or rate of SARS-CoV-2 clearance between RDV-treated and placebo-treated patients;

Study Design	Methods	Results	Limitations and Interpretation
Remdesivir Versus Placebo for Severe COVID-19 in China[2], continued			
	Interventions: • IV RDV 200 mg on Day 1, then 100 mg daily for 9 days • Saline placebo for 10 days **Primary Endpoint:** • Time to clinical improvement, defined as improvement on an ordinal scale or being discharged alive from the hospital	• Receipt of IFN alfa-2b: 29% of patients in RDV arm, 38% in placebo arm **Outcomes:** • No difference in time to clinical improvement between RDV and placebo arms (median time 21 days vs. 23 days; HR 1.23; 95% CI, 0.87–1.75). • For patients who started RDV or placebo within 10 days of symptom onset, faster time to clinical improvement was seen with RDV (median time 18 days vs. 23 days; HR 1.52; 95% CI, 0.95–2.43); however, this was not statistically significant. • 28-day mortality was similar between arms (14% of patients in RDV arm, 13% in placebo arm). • No difference between arms in SARS-CoV-2 viral load at baseline, and rate of decline over time was similar. • Percentage of patients with AEs: 66% in RDV arm, 64% in placebo arm • Discontinuations due to AEs: 12% of patients in RDV arm, 5% in placebo arm	however, study was underpowered to detect differences in these outcomes between arms.
World Health Organization Solidarity Trial[3]			
International, open-label, adaptive RCT with multiple treatment arms that enrolled hospitalized patients with COVID-19 (n = 11,330). In 1 arm, patients received RDV.	**Key Inclusion Criteria:** • Aged ≥18 years • Not known to have received any study drug • Not expected to be transferred elsewhere within 72 hours • Physician reported no contraindications to study drugs **Interventions:** • IV RDV 200 mg on Day 0, then 100 mg daily on Days 1–9 • Local SOC	**Number of Participants:** • ITT analysis: RDV (n = 2,743) and SOC (n = 2,708) **Participant Characteristics:** • Percentage of patients aged 50–69 years: 47% in RDV arm, 48% in SOC arm • Percentage of patients aged ≥70 years: 18% in RDV arm, 17% in SOC arm • 67% of patients in both arms were on supplemental oxygen at entry. • 9% of patients in both arms were mechanically ventilated at entry.	**Limitations:** • Open-label study design limits the ability to assess time to recovery; clinicians and patients were aware of treatment assignment, so RDV may have been continued to complete the treatment course even if the patient had improved. • No data on time from symptom onset to enrollment • No assessment of outcomes post hospital discharge

Study Design	Methods	Results	Limitations and Interpretation
World Health Organization Solidarity Trial[3], continued			

	Primary Endpoint:
	• In-hospital mortality
	Secondary Endpoints:
	• Initiation of mechanical ventilation
	• Duration of hospitalization
		• Percentage of patients hospitalized for ≥2 days at entry: 40% in RDV arm, 39% in SOC arm
		• Percentages of patients with comorbid conditions were similar between RDV and SOC arms: diabetes (26% and 25%), heart disease (21% both groups), and chronic lung disease (6% and 5%).
		• 48% of patients in both arms received corticosteroids.
		Primary Outcomes:
		• In-hospital mortality: 301 deaths (11.0%) in RDV arm, 303 deaths (11.2%) in SOC arm
		• Rate ratios for in-hospital death:
		  • Overall: 0.95 (95% CI, 0.81–1.11)
		  • No mechanical ventilation at entry: 0.86 (99% CI, 0.67–1.11)
		  • Mechanical ventilation at entry: 1.20 (99% CI, 0.80–1.80)
		Secondary Outcomes:
		• Initiation of mechanical ventilation: 295 patients (10.8%) in RDV arm, 284 patients (10.5%) in SOC arm
			Interpretation:
			• RDV did not decrease in-hospital mortality in hospitalized patients when compared to local SOC.

Remdesivir Versus Standard of Care in Hospitalized Patients with Moderate COVID-19[4]			
Open-label randomized trial in hospitalized patients (n = 596)	**Key Inclusion Criteria:** • Laboratory-confirmed SARS-CoV-2 infection • Moderate pneumonia, defined as radiographic evidence of pulmonary infiltrates and SpO_2 >94% on room air **Key Exclusion Criteria:** • ALT or AST >5 times ULN • CrCl <50 mL/min	**Number of Participants:** • 584 patients began treatment: 10-day RDV (n = 193), 5-day RDV (n = 191), and SOC (n = 200) **Participant Characteristics:** • Demographic and baseline disease characteristics were similar across all arms. **Outcomes:** • 5-day RDV had significantly higher odds of better clinical status distribution on Day 11 than SOC (OR 1.65; 95% CI, 1.09–2.48; $P = 0.02$).	**Limitations:** • Open-label design may have affected decisions related to concomitant medication use and hospital discharge. • Greater proportion of patients in SOC arm received HCQ, LPV/RTV, or AZM, which may cause AEs and have not shown clinical benefits in hospitalized patients with COVID-19.

Study Design	Methods	Results	Limitations and Interpretation
Remdesivir Versus Standard of Care in Hospitalized Patients with Moderate COVID-19[4], continued			
	Interventions: • IV RDV 200 mg on Day 1, then 100 mg daily for 9 days • IV RDV 200 mg on Day 1, then 100 mg daily for 4 days • Local SOC **Primary Endpoint:** • Clinical status on Day 11, as measured by a 7-point ordinal scale	• Clinical status distribution on Day 11 was not significantly different between the 10-day RDV and SOC arms ($P = 0.18$). • By Day 28, there were more hospital discharges among patients who received RDV (89% in 5-day arm and 90% in 10-day arm) than those who received SOC (83%). • Mortality was low in all arms (1% to 2%). • Percentages of patients with AEs in RDV arms vs. SOC arm: nausea (10% vs. 3%), hypokalemia (6% vs. 2%), and headache (5% vs. 3%)	• No data on time to return to activity for discharged patients **Interpretation:** • Hospitalized patients with moderate COVID-19 who received 5 days of RDV had better outcomes than those who received SOC; however, difference between arms was of uncertain clinical importance.
Different Durations of Remdesivir Treatment in Hospitalized Patients[5]			
Manufacturer-sponsored, multinational, randomized, open-label trial in hospitalized patients with COVID-19 (n = 402)	**Key Inclusion Criteria:** • Aged ≥12 years • Laboratory-confirmed SARS-CoV-2 infection • Radiographic evidence of pulmonary infiltrates • SpO_2 ≤94% on room air or receipt of supplemental oxygen **Key Exclusion Criteria:** • Receipt of mechanical ventilation or ECMO • Multiorgan failure • ALT or AST >5 times ULN • Estimated CrCl <50 mL/min **Interventions:** • IV RDV 200 mg on Day 1, then 100 mg daily for 4 days • IV RDV 200 mg on Day 1, then 100 mg daily for 9 days **Primary Endpoint:** • Clinical status at Day 14, as measured by a 7-point ordinal scale	**Number of Participants:** • 397 participants began treatment: 5-day RDV (n = 200) and 10-day RDV (n = 197) **Participant Characteristics:** • At baseline, patients in 10-day arm had worse clinical status (based on ordinal scale distribution) than those in 5-day arm ($P = 0.02$) **Outcomes:** • After adjusting for imbalances in baseline clinical status, Day 14 distribution in clinical status on the ordinal scale was similar between arms ($P = 0.14$). • Time to achieve clinical improvement of at least 2 levels on the ordinal scale (median day of 50% cumulative incidence) was similar between arms (10 days vs. 11 days). • Median durations of hospitalization among patients discharged on or before Day 14 were similar between 5-day (7 days; IQR 6–10 days) and 10-day arms (8 days; IQR 5–10 days). • Percentages of patients with SAEs: 35% in 10-day arm, 21% in 5-day arm	**Limitations:** • This was an open-label trial without a placebo control arm, so clinical benefit of RDV (compared with no RDV) could not be assessed. • There were baseline imbalances in clinical status of patients in the 5-day and 10-day arms. **Interpretation:** • In hospitalized patients with severe COVID-19 who were not on mechanical ventilation or ECMO, RDV treatment for 5 or 10 days had a similar clinical benefit.

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

Key: AE = adverse effects; ALT = alanine transaminase; AST = aspartate aminotransferase; AZM = azithromycin; CrCl = creatinine clearance; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; HCQ = hydroxychloroquine; IFN = interferon; ITT = intention to treat; IV = intravenous; LPV/RTV = lopinavir/ritonavir; the Panel = the COVID-19 Treatment Guidelines Panel; PaO_2/FiO_2 = ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; RCT = randomized controlled trial; RDV = remdesivir; RRR = recovery rate ratio; SAE = serious adverse effects; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOC = standard of care; SpO_2 = saturation of oxygen; ULN = upper limit of normal

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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 **(AIIa)**.
- The Panel **recommends against** the use of **high-dose chloroquine** (600 mg twice daily for 10 days) for the treatment of COVID-19 **(AI)**.

Rationale

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

In a large randomized controlled trial of hospitalized patients in the United Kingdom, hydroxychloroquine did not decrease 28-day mortality when compared to the usual standard of care. Participants who were randomized to receive hydroxychloroquine had a longer median hospital stay than those who received the standard of care. In addition, among patients who were not on invasive mechanical ventilation at the time of randomization, those who received hydroxychloroquine were more likely to subsequently require intubation or die during hospitalization than those who received the standard of care.[5]

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

In addition to these randomized trials, data from large retrospective observational studies do not consistently show evidence of a benefit for hydroxychloroquine with or without azithromycin in hospitalized patients with COVID-19. For example, in a large retrospective observational study of patients who were hospitalized with COVID-19, hydroxychloroquine use was not associated with a reduced risk of death or mechanical ventilation.[8] Another multicenter retrospective observational study evaluated the use of hydroxychloroquine with and without azithromycin in a random sample of a large cohort of hospitalized patients with COVID-19.[9] Patients who received hydroxychloroquine with or without azithromycin did not have a decreased risk of in-hospital mortality when compared to those who received neither hydroxychloroquine nor azithromycin.

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

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

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

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

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

Please see Table 2b for additional details.

Adverse Effects

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

Cardiac Adverse Effects

- QTc prolongation, Torsade de Pointes, ventricular 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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Table 2b. Chloroquine or Hydroxychloroquine With or Without Azithromycin: Selected Clinical Data

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

The Panel has reviewed other clinical studies of HCQ with or without AZM and studies of CQ for the treatment of COVID-19.[1-11] These studies have limitations that make them less definitive and informative than the studies discussed here. The Panel's summaries and interpretations of some of those studies are available in the archived versions of the COVID-19 Treatment Guidelines.

Study Design	Methods	Results	Limitations and Interpretation
Randomised Evaluation of COVID-19 Therapy (RECOVERY) Trial[12]			
Open-label RCT with multiple arms, including a control arm; in 1 arm, hospitalized patients received HCQ (n = 11,197) *This is a preliminary report that has not yet been peer reviewed.*	**Key Inclusion Criteria:** • Clinically suspected or laboratory-confirmed SARS-CoV-2 infection **Key Exclusion Criteria:** • Patients with prolonged QTc intervals were excluded from HCQ arm. **Interventions:** • HCQ 800 mg at entry and at 6 hours, then HCQ 400 mg every 12 hours for 9 days or until discharge • Usual SOC **Primary Endpoint:** • All-cause mortality at Day 28 after randomization	**Number of Participants:** • HCQ (n = 1,561) and SOC (n = 3,155) • Study enrollment ended early after investigators and trial-steering committee concluded that the data showed no benefit for HCQ. **Participant Characteristics:** • Mean age was 65 years in both arms; 41% of patients were aged ≥70 years. • 90% of patients had laboratory-confirmed SARS-CoV-2 infection. • 57% of patients had ≥1 major comorbidity: 27% had diabetes mellitus, 26% had heart disease, and 22% had chronic lung disease. • At randomization, 17% of patients were receiving invasive mechanical ventilation or ECMO, 60% were receiving oxygen only (with or without noninvasive ventilation), and 24% were receiving neither. • Use of AZM or another macrolide during the follow-up period was similar in both arms, as was use of dexamethasone.	**Limitations:** • Not blinded • Information on occurrence of new major cardiac arrythmia was not collected throughout the trial. **Interpretation:** • HCQ does not decrease 28-day all-cause mortality when compared to the usual SOC in hospitalized patients with clinically suspected or laboratory-confirmed SARS-CoV-2 infection. • Patients who received HCQ had a longer median length of hospital stay, and those who were not on invasive mechanical ventilation at the time of randomization were more likely to require intubation or die during hospitalization if they received HCQ.

Study Design	Methods	Results	Limitations and Interpretation
Randomised Evaluation of COVID-19 Therapy (RECOVERY) Trial[12], continued			
		Outcomes: • No significant difference in 28-day mortality between the 2 arms; 418 patients (26.8%) in HCQ arm and 788 patients (25.0%) in SOC arm had died by Day 28 (RR 1.09; 95% CI, 0.96–1.23; *P* = 0.18). • A similar 28-day mortality for HCQ patients was reported during the post hoc exploratory analysis that was restricted to the 4,234 participants (90%) who had a positive SARS-CoV-2 test result. • Patients in HCQ arm were less likely to survive hospitalization and had a longer median time to discharge than patients in SOC arm. • Patients who received HCQ and who were not on invasive mechanical ventilation at baseline had an increased risk of requiring intubation and an increased risk of death. • At the beginning of the study, the researchers did not record whether a patient developed a major cardiac arrhythmia after study enrollment; however, these data were later collected for 698 patients (44.7%) in HCQ arm and 1,357 patients (43.0%) in SOC arm. • No differences between the arms in the frequency of supraventricular tachycardia, ventricular tachycardia or fibrillation, or instances of AV block that required intervention.	
Hydroxychloroquine and Hydroxychloroquine Plus Azithromycin for Mild or Moderate COVID-19[13]			
Open-label, 3-arm RCT in hospitalized patients (n = 667)	**Key Inclusion Criteria:** • Aged ≥18 years • Clinically suspected or laboratory-confirmed SARS-CoV-2 infection • Mild or moderate COVID-19 • Duration of symptoms ≤14 days	**Number of Participants:** • Modified ITT analysis included patients with laboratory-confirmed SARS-CoV-2 infection (n = 504). **Participant Characteristics:** • Mean age was 50 years. • 58% of patients were men. • At baseline, 58.2% of patients were ordinal level 3; 41.8% were ordinal level 4. • Median time from symptom onset to randomization was 7 days.	**Limitations:** • Not blinded • Follow-up period was restricted to 15 days. **Interpretation:** • Neither HCQ alone nor HCQ plus AZM improved clinical outcomes at Day 15 after randomization among hospitalized patients with mild or moderate COVID-19.

Study Design	Methods	Results	Limitations and Interpretation
Hydroxychloroquine and Hydroxychloroquine Plus Azithromycin for Mild or Moderate COVID-19[13], continued			
	Key Exclusion Criteria: • Need for >4 L of supplemental oxygen or ≥40% FiO_2 by face mask • History of ventricular tachycardia • QT interval ≥480 ms **Interventions:** • HCQ 400 mg twice daily for 7 days plus SOC • HCQ 400 mg twice daily plus AZM 500 mg daily for 7 days plus SOC • SOC alone **Primary Endpoint:** • Clinical status at Day 15, as assessed by a 7-point ordinal scale among the patients with confirmed SARS-CoV-2 infection **Ordinal Scale Definitions:** 1. Not hospitalized, no limitations 2. Not hospitalized, with limitations 3. Hospitalized, not on oxygen 4. Hospitalized, on oxygen 5. Hospitalized, oxygen administered by HFNC or noninvasive ventilation 6. Hospitalized, on mechanical ventilation 7. Death	• 23.3% to 23.9% of patients received oseltamivir. **Outcomes:** • No significant difference between the odds of worse clinical status at Day 15 for patients in HCQ arm (OR 1.21; 95% CI, 0.69–2.11; $P = 1.00$) and patients in HCQ plus AZM arm (OR 0.99; 95% CI, 0.57–1.73; $P = 1.00$). • No significant differences in secondary outcomes of the 3 arms, including progression to mechanical ventilation during the first 15 days and mean number of days "alive and free of respiratory support." • A greater proportion of patients in HCQ plus AZM arm (39.3%) and HCQ arm (33.7%) experienced AEs than those in SOC arm (22.6%). • QT prolongation was more common in patients who received HCQ plus AZM or HCQ alone than in patients who received SOC alone, but fewer patients in SOC arm had serial electrocardiographic studies performed during the follow-up period.	

Study Design	Methods	Results	Limitations and Interpretation
Hydroxychloroquine Versus Standard of Care for Mild or Moderate COVID-19[14]			
Multicenter, randomized, open-label trial (n = 150)	**Key Inclusion Criteria:** • Aged ≥18 years • Laboratory-confirmed SARS-CoV-2 infection **Key Exclusion Criteria:** • Severe conditions, including heart, liver, or kidney disease • Inability to take oral medications • Pregnancy or breastfeeding **Interventions:** • HCQ 1,200 mg once daily for 3 days, then HCQ 800 mg once daily for 2 weeks (in patients with mild or moderate COVID-19) or 3 weeks (in patients with severe disease) • SOC **Primary Endpoint:** • Negative conversion of SARS-CoV-2 by Day 28	**Number of Participants:** • HCQ (n = 75) and SOC (n = 75) **Participant Characteristics:** • Patients were randomized at a mean of 16.6 days after symptom onset. • 99% of patients had mild or moderate COVID-19. **Outcomes:** • HCQ arm and SOC arm had similar negative PCR conversion rates within 28 days (85.4% of participants vs. 81.3% of participants) and similar times to negative PCR conversion (median of 8 days vs. 7 days). • No difference in the probability of symptom alleviation between the arms in the ITT analysis.	**Limitations:** • Unclear how the overall rate of symptom alleviation was calculated • Study did not reach target sample size. **Interpretation:** • This study demonstrated no difference in the rate of viral clearance between HCQ and SOC.
High-Dose Chloroquine Versus Low-Dose Chloroquine[15]			

Randomized, double-blind, Phase 2b study in hospitalized adults (n = 81)	**Key Inclusion Criteria:**
	• Aged ≥18 years
	• Clinically suspected COVID-19
	• At least 1 of the following conditions:
	  • Respiratory rate >24 rpm
	  • Heart rate >125 bpm
	  • SpO_2 <90% on room air
	  • Shock
		Number of Participants:
		• High-dose CQ (n = 41) and low-dose CQ (n = 40)
		• Planned study sample size was 440 participants, but study was stopped by the study's DSMB.
		Participant Characteristics:
		• All patients also received ceftriaxone plus AZM.
		• 89.6% of patients received oseltamivir.
			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 CQ is administered in combination with AZM and oseltamivir.

Study Design	Methods	Results	Limitations and Interpretation
High-Dose Chloroquine Versus Low-Dose Chloroquine[15], continued			
	Interventions: • CQ 600 mg twice daily for 10 days (high dose) • CQ 450 mg twice daily for 1 day, then CQ 450 mg for 4 days (low dose) **Primary Endpoint:** • Mortality by Day 28	**Outcomes:** • Overall fatality rate was 27.2%. • Mortality by Day 13 was higher in high-dose arm than in low-dose arm (death occurred in 16 of 41 patients [39%] vs. in 6 of 40 patients [15%]; $P = 0.03$). This difference was no longer significant after controlling for age (OR 2.8; 95% CI, 0.9–8.5). • Overall, QTcF >500 ms occurred more frequently in high-dose arm (18.9% of patients) than in low-dose arm (11.1%). • In the high-dose arm, 2 patients experienced ventricular tachycardia before death.	
Hydroxychloroquine in Nonhospitalized Adults with Early COVID-19[16]			
Randomized, placebo-controlled trial in the United States and Canada (n = 491)	**Key Inclusion Criteria:** • ≤4 days of symptoms that were compatible with COVID-19 • Either laboratory-confirmed SARS-CoV-2 infection or high-risk exposure within the previous 14 days **Key Exclusion Criteria:** • Aged <18 years • Hospitalized • Receipt of certain medications **Interventions:** • HCQ 800 mg once, then HCQ 600 mg in 6 to 8 hours, then HCQ 600 mg once daily for 4 days • Placebo	**Number of Participants:** • Contributed to primary endpoint data: HCQ (n = 212) and placebo (n = 211) **Participant Characteristics:** • 241 patients were exposed to people with COVID-19 through their position as health care workers (57%), 106 were exposed through household contacts (25%), and 76 had other types of exposure (18%). • Median age was 40 years. • 56% of patients were women. • Only 3% of patients were Black. • Very few patients had comorbidities: 11% had hypertension, 4% had diabetes, and 68% had no chronic medical conditions. • 56% of patients were enrolled on Day 1 of symptom onset. • 341 participants (81%) had either a positive PCR result or a high-risk exposure to a PCR-positive contact.	**Limitations:** • This study enrolled a highly heterogenous population. • Only 227 of 423 participants (53.7%) were confirmed PCR-positive for SARS-CoV-2. • Changing the primary endpoint without a new power calculation makes it difficult to assess whether the study is powered to detect differences in outcomes between the study arms. • This study used surveys for screening, symptom assessment, and adherence reporting. • Visual analog scales are not commonly used, and their ability to assess acute viral respiratory infections in clinical trials has not been validated.

Study Design	Methods	Results	Limitations and Interpretation
Hydroxychloroquine in Nonhospitalized Adults with Early COVID-19[16], continued			
	Primary Endpoints: • Planned primary endpoint was ordinal outcome by Day 14 in 4 categories: not hospitalized, hospitalized, ICU stay, or death. • Because event rates were lower than expected, a new primary endpoint was defined: change in overall symptom severity over 14 days, assessed on a 10-point, self-reported, visual analog scale	**Outcomes:** • Compared to the placebo recipients, HCQ recipients had a nonsignificant 12% difference in improvement in symptoms between baseline and Day 14 (-2.60 vs. -2.33 points; $P = 0.117$). • Ongoing symptoms were reported by 24% of those in HCQ arm and 30% of those in the placebo arm at Day 14 ($P = 0.21$). • No difference in the incidence of hospitalization (4 patients in the HCQ arm vs. 10 patients in placebo arm); 2 of 10 placebo participants were hospitalized for reasons that were unrelated to COVID-19. • A higher percentage of patients in HCQ arm experienced AEs than patients in placebo arm (43% vs. 22%; $P < 0.001$).	**Interpretation:** • The study has some limitations, and it did not find evidence that early administration of HCQ reduced symptom severity in patients with mild COVID-19.
Hydroxychloroquine in Nonhospitalized Adults with Mild COVID-19[17]			
Open-label RCT in Spain (n = 353)	**Key Inclusion Criteria:** • Laboratory-confirmed SARS-CoV-2 infection • <5 days of mild COVID-19 symptoms **Key Exclusion Criteria:** • Moderate to severe COVID-19 • Severe liver or renal disease • History of cardiac arrhythmia • QT prolongation **Interventions:** • HCQ 800 mg on Day 1, then HCQ 400 mg once daily for 6 days • No antiviral treatment	**Number of Participants:** • ITT analysis: HCQ (n = 136) and control (n = 157) • 60 patients were excluded from the ITT analysis due to negative baseline RT-PCR, missing RT-PCR at follow-up visits, or consent withdrawal. **Participant Characteristics:** • Mean age was 41.6 years. • 67% of patients were woman. • Majority of patients were health care workers (87%). • 53% of patients reported chronic health conditions. • Median time from symptom onset to enrollment was 3 days (IQR 2–4 days). • Most common COVID-19 symptoms were fever, cough, and sudden olfactory loss.	**Limitations:** • Open-label, non-placebo-controlled trial • Study design allowed for the possibility of drop-outs in control arm and over-reporting of AEs in HCQ arm. • The intervention changed during the study; the authors initially planned to include HCQ plus DRV/COBI. • The majority of the participants were relatively young health care workers. **Interpretation:** • Early administration of HCQ to patients with mild COVID-19 did not result in improvement in virologic clearance, a lower risk of disease progression, or a reduced time to symptom improvement.

Study Design	Methods	Results	Limitations and Interpretation
Hydroxychloroquine in Nonhospitalized Adults with Mild COVID-19[17], continued			
	Primary Endpoint: • Reduction in SARS-CoV-2 viral load, assessed using nasopharyngeal swabs on Days 3 and 7 **Secondary Endpoints:** • Disease progression up to Day 28 • Time to complete resolution of symptoms	**Outcomes:** • No significant difference in viral load reduction between control arm and HCQ arm 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). • No difference in the risk of hospitalization between control arm and HCQ arm (7.1% vs. 5.9%; risk ratio 0.75; 95% CI, 0.32–1.77). • No difference in the median time from randomization to the resolution of COVID-19 symptoms between the 2 arms (12.0 days in control arm vs. 10.0 days in HCQ arm; $P = 0.38$). • A higher percentage of participants in the HCQ arm than in the control arm experienced AEs during the 28-day follow-up period (72% vs. 9%). Most common AEs were GI disorders and "nervous system disorders." • SAEs were reported in 12 patients in control arm and 8 patients in HCQ arm. SAEs that occurred among patients in HCQ arm were not deemed to be related to the drug.	
Observational Study on Hydroxychloroquine With or Without Azithromycin[18]			
Retrospective, multicenter, observational study in a random sample of inpatients with COVID-19 from the New York Department of Health (n = 1,438)	**Key Inclusion Criteria:** • Laboratory-confirmed SARS-CoV-2 infection **Interventions:** • HCQ plus AZM • HCQ alone • AZM alone • Neither drug **Primary Endpoint:** • In-hospital mortality	**Number of Participants:** • HCQ plus AZM (n = 735), HCQ alone (n = 271), AZM alone (n = 211), and neither drug (n = 221) **Participant Characteristics:** • Patients in the treatment arms had more severe disease at baseline than those who received neither drug. **Outcomes:** • In adjusted analyses, patients who received 1 of the 3 treatment regimens did not show a decreased in-hospital mortality rate when compared with those who received neither drug.	**Limitations:** • This study has the inherent limitations of an observational study, including residual confounding from confounding variables that were unrecognized and/or unavailable for analysis. **Interpretation:** • Despite the limitations discussed above, these findings suggest that although HCQ and AZM are not associated with an increased risk of

Study Design	Methods	Results	Limitations and Interpretation
Observational Study on Hydroxychloroquine With or Without Azithromycin[18], continued			
	Secondary Endpoint: • Cardiac arrest and arrhythmia or QT prolongation on an ECG	• Patients who received HCQ plus AZM had a greater risk of cardiac arrest than patients who received neither drug (OR 2.13; 95% CI, 1.12–4.05).	in-hospital death, the combination of HCQ and AZM may be associated with an increased risk of cardiac arrest.
Observational Study of Hydroxychloroquine Versus No Hydroxychloroquine in New York City[19]			
Observational study in hospitalized adults with COVID-19 at a large medical center (n = 1,376)	**Key Inclusion Criteria:** • Laboratory-confirmed SARS-CoV-2 infection **Key Exclusion Criteria:** • Intubation, death, or transfer to another facility within 24 hours of arriving at the emergency department **Interventions:** • HCQ 600 mg twice daily on Day 1, then HCQ 400 mg once daily for 4 days • No HCQ **Primary Endpoint:** • Time from study baseline (24 hours after patients arrived at the emergency department) to intubation or death	**Number of Participants:** • Received HCQ (n = 811) and did not receive HCQ (n = 565) **Participant Characteristics:** • HCQ recipients were more severely ill at baseline than those who did not receive HCQ. **Outcomes:** • Using propensity scores to adjust for major predictors of respiratory failure and inverse probability weighting, the study demonstrated that HCQ use was not associated with intubation or death (HR 1.04; 95% CI, 0.82–1.32). • No association between concomitant use of AZM and the composite endpoint of intubation or death (HR 1.03; 95% CI, 0.81–1.31).	**Limitations:** • This study has the inherent limitations of an observational study, including residual confounding from confounding variables that were unrecognized and/or unavailable for analysis. **Interpretation:** • The use of HCQ for treatment of COVID-19 was not associated with harm or benefit in a large observational study.
Observational Cohort Study of Hydroxychloroquine Versus No Hydroxychloroquine in France[20]			
Retrospective, observational cohort study in hospitalized adults with severe COVID-19 pneumonia at 4 tertiary care centers (n = 181)	**Key Inclusion Criteria:** • Aged 18 to 80 years • Laboratory-confirmed SARS-CoV-2 infection • Required supplemental oxygen **Key Exclusion Criteria:** • Started HCQ before hospital admission	**Number of Participants:** • Received HCQ within 48 hours (n = 84), received HCQ beyond 48 hours (n = 8), and did not receive HCQ (n = 89) **Participant Characteristics:** • In the HCQ arm, 18% of patients received concomitant AZM.	**Limitations:** • This was a retrospective, nonrandomized study. **Interpretation:** • There was no difference in the rates of clinically important outcomes between patients who received HCQ within 48 hours of hospital admission and those who did not.

Study Design	Methods	Results	Limitations and Interpretation
Observational Cohort Study of Hydroxychloroquine Versus No Hydroxychloroquine in France[20], continued			
	• Received tocilizumab, LPV/RTV, or RDV within 48 hours of admission • Organ failure requiring immediate ICU admission • ARDS **Interventions:** • HCQ 600 mg once daily • No HCQ **Primary Endpoint:** • Survival without transfer to the ICU at Day 21 **Secondary Endpoints:** • Overall survival rate at Day 21 • Survival rate without ARDS at Day 21 • Weaning from oxygen by Day 21 • Discharge from hospital to home or rehabilitation by Day 21	**Outcomes:** • In the inverse probability of treatment-weighted analysis, there was no difference in survival rates without ICU transfer at Day 21 between the HCQ arm (76% of participants) and the non-HCQ arm (75%). • No difference between the arms in the secondary outcomes of overall survival rate and survival rate without ARDS at Day 21.	
Retrospective Cohort Study of Hydroxychloroquine Versus No Hydroxychloroquine in Detroit, Michigan[21]			
Comparative, retrospective cohort study in hospitalized patients with COVID-19 in the Henry Ford Health System in Michigan (n = 2,541)	**Key Inclusion Criteria:** • Laboratory-confirmed SARS-CoV-2 infection **Interventions:** • HCQ 400 mg twice daily for 1 day, then 200 mg twice daily for 4 days • AZM 500 mg for 1 day, then 250 mg once daily for 4 days • HCQ plus AZM, at the above doses • Neither drug	**Number of Participants:** • HCQ alone (n = 1,202), AZM alone (n = 147), HCQ plus AZM (n = 783), and neither drug (n = 409) **Participant Characteristics:** • HCQ plus AZM was reserved for patients with severe COVID-19 and minimal cardiac risks. • Median patient age was 64 years (IQR 53–76 years); 51% of patients were men, 56% were African American, and 52% had a BMI ≥30. • Median time to follow-up was 28.5 days (IQR 3–53 days).	**Limitations:** • This study evaluated 1 health care system with an institutional protocol for HCQ and AZM use. • Because the study was not randomized and not blinded, there is a possibility of residual confounding. • There was a lower rate of ICU admission among patients who did not receive HCQ, which suggests that this group may have received less aggressive care.

Study Design	Methods	Results	Limitations and Interpretation
Retrospective Cohort Study of Hydroxychloroquine Versus No Hydroxychloroquine in Detroit, Michigan[21], continued			
	Primary Endpoint: • In-hospital mortality	• The mSOFA score was not available for 25% of patients. • Corticosteroids were given to 79% of patients in the HCQ alone arm, 74% of patients in the HCQ plus AZM arm, and 35.7% of those on neither drug. **Outcomes:** • Overall, crude mortality was 18.1%. When broken down by the different arms, mortality was 13.5% in HCQ alone arm, 20.1% in HCQ plus AZM arm, 22.4% in AZM alone arm, and 26.4% in the arm that received neither drug ($P < 0.001$). • Mortality HRs were analyzed using a multivariable Cox regression model; the arm that received neither drug was used as the reference. HCQ alone decreased the mortality HR by 66% ($P < 0.001$). HCQ plus AZM decreased the mortality HR by 71% ($P < 0.001$). • Other predictors of mortality were age ≥65 years (HR 2.6; 95% CI, 1.9–3.3); White race (HR 1.7; 95% CI, 1.4–2.1); chronic kidney disease (HR 1.7; 95% CI, 1.4–2.1); reduced 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 HCQ (95% CI, 0.285–0.832, $P = 0.009$).	• Given that the RECOVERY trial showed that dexamethasone use conferred a survival benefit, it is possible that the findings were confounded by the imbalance in corticosteroid use among the arms. **Interpretation:** • This study reported a mortality benefit in hospitalized patients with COVID-19 who received either HCQ alone or HCQ plus AZM compared to patients who received neither drug. However, there were substantial imbalances in corticosteroid use among the arms, which may have affected mortality. • Because the study was retrospective and observational, it cannot control for confounders.

Key: AE = adverse effect; ARDS = acute respiratory distress syndrome; AV = atrioventricular; AZM = azithromycin; BMI = body mass index; bpm = beats per minute; CQ = chloroquine; DRV/COBI = darunavir/cobicistat; DSMB = data safety monitoring board; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; FiO_2 = fraction of inspired oxygen; GI = gastrointestinal; HCQ = hydroxychloroquine; HFNC = high-flow nasal cannula; ICU = intensive care unit; ITT = intention to treat; LPV/RTV = lopinavir/ritonavir; mSOFA = modified sequential organ failure assessment; the Panel = the COVID-19 Treatment Guidelines Panel; PCR = polymerase chain reaction; QTcF = Fridericia's correction formula; RCT = randomized controlled trial; RDV = remdesivir; RR = rate ratio; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse effect; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOC = standard of care

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Ivermectin

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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 is generally well tolerated.[1,3] Ivermectin is not approved by the FDA for the treatment of any viral infection.

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

Reports from in vitro studies suggest that ivermectin acts by inhibiting the host importin alpha/beta-1 nuclear transport proteins, which are part of a key intracellular transport process that viruses hijack to enhance infection by suppressing the host's antiviral response.[4,5] In addition, ivermectin docking may interfere with the attachment of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein to the human cell membrane.[6] Ivermectin is thought to be a host-directed agent, which may be the basis for its broad-spectrum activity in vitro against the viruses that cause dengue, Zika, HIV, and yellow fever.[4,7-9] Despite this in vitro activity, no clinical trials have reported a clinical benefit for ivermectin in patients with these viruses. Some studies of ivermectin have also reported potential anti-inflammatory properties, which have been postulated to be beneficial in people with COVID-19.[10-12]

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

Recommendation

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

Rationale

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

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

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

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

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

Monitoring, Adverse Effects, and Drug-Drug Interactions

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

Considerations in Pregnancy

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

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

Considerations in Children

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

Clinical Trials

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

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Table 2c. Ivermectin: Selected Clinical Data

Last Updated: February 11, 2021

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

Study Design	Methods	Results	Limitations and Interpretation
Ivermectin Versus Ivermectin Plus Doxycycline Versus Placebo for Treatment of COVID-19[1]			
Randomized, double-blind, placebo-controlled trial of hospitalized adults in Dhaka, Bangladesh (n = 72)	**Key Inclusion Criteria:** • Aged 18–65 years • Laboratory-confirmed SARS-CoV-2 infection with fever, cough, or sore throat • Admitted to hospital within previous 7 days **Key Exclusion Criteria:** • Chronic cardiac, renal, or liver disease **Interventions:** • IVM 12 mg PO once daily for 5 days • Single dose of IVM 12 mg PO plus DOX 200 mg PO on Day 1, then DOX 100 mg every 12 hours for 4 days • Placebo **Primary Endpoints:** • Time to virologic clearance, measured by obtaining an NP swab for SARS-CoV-2 PCR on Days 3, 7, and 14, then weekly until PCR result was negative • Resolution of fever and cough within 7 days	**Number of Participants:** • IVM (n = 24; 2 withdrew), IVM plus DOX (n = 24; 1 withdrew), and placebo (n = 24; 1 withdrew) **Participant Characteristics:** • Mean age was 42 years. • 54% of participants were female. • Mean time from symptom onset to assessment was 3.83 days. • No patients required supplemental oxygen. **Primary Outcomes:** • Shorter mean time to virologic clearance with IVM than placebo (9.7 days vs. 12.7 days; $P = 0.02$), but not with IVM plus DOX (11.5 days; $P = 0.27$). • Rates of virologic clearance were greater in IVM arm at Day 7 (HR 4.1; 95% CI, 1.1–14.7; $P = 0.03$) and at Day 14 (HR 2.7; 95% CI, 1.2–6.0; $P = 0.02$) compared to placebo, but not in the IVM plus DOX arm (HR 2.3; 95% CI, 0.6–9.0; $P = 0.22$ and HR 1.7; 95% CI, 0.8–4.0; $P = 0.19$). • No statistically significant difference in time to resolution of fever, cough, or sore throat between IVM and placebo arms ($P = 0.35$, $P = 0.18$, and $P = 0.35$, respectively) or IVM plus DOX and placebo arms (P = 0.09, $P = 0.23$, and $P = 0.09$, respectively). **Other Outcomes:** • Mean values of CRP, LDH, procalcitonin, and ferritin declined in all arms from baseline to Day 7, but there were no between-arm comparisons of the changes. • No between-arm differences in duration of hospitalization ($P = 0.93$). • No SAEs recorded.	**Limitations:** • Small sample size • Not clear whether both IVM and DOX placebos were used. • Patients with chronic diseases were excluded. • Disease appears to have been mild in all participants; thus, the reason for hospitalization is unclear. • Absolute changes in inflammatory markers are not presented but were reportedly significant. • PCR results are not a validated surrogate marker for clinical efficacy. **Interpretation:** • A 5-day course of IVM resulted in faster virologic clearance than placebo, but not a faster time to resolution of symptoms (fever, cough, and sore throat). Because time to virologic clearance is not a validated surrogate marker for clinical efficacy, the clinical efficacy of IVM is unknown.

Study Design	Methods	Results	Limitations and Interpretation
Ivermectin Versus Placebo for Outpatients With Mild COVID-19[2]			
Open-label RCT of adult outpatients in Lahore, Pakistan (n = 50)	**Key Inclusion Criteria:** • SARS-CoV-2 PCR positive • Mild disease **Key Exclusion Criteria:** • Severe symptoms likely related to cytokine storm • Malignancy, chronic kidney disease, or cirrhosis • Pregnancy **Interventions:** • IVM 12 mg PO immediately, followed by 12 mg doses at 12 and 24 hours, plus symptomatic treatment • Symptomatic treatment **Primary Endpoint:** • Symptoms reported on Day 7. Patients were stratified as asymptomatic or symptomatic.	**Number of Participants:** • IVM (n = 25) and control (n = 25) **Participant Characteristics:** • Mean age was 40.6 years. • 62% of participants were male. • 40% of participants had diabetes, 30% were smokers, 26% had hypertension, 8% had cardiovascular disease, and 12% had obesity. **Outcomes:** • Proportion of asymptomatic patients at Day 7 was similar in IVM and control arms (64% vs. 60%; $P = 0.500$). • AEs were attributed to IVM in 8 patients (32%).	**Limitations:** • Small sample size • Open-label study • Authors reported the proportions of participants with certain symptoms and comorbidities but did not provide objective assessment of disease severity. This precludes the ability to compare outcomes between arms. • Study classified outcomes at Day 7 as "symptomatic" and "asymptomatic," but did not account for symptom worsening or improvement. **Interpretation:** • IVM showed no effect on symptom resolution in patients with mild COVID-19.
Ivermectin Plus Doxycycline Versus Hydroxychloroquine Plus Azithromycin for Asymptomatic Patients and Patients with Mild to Moderate COVID-19[3]			
RCT of outpatients with SARS-CoV-2 infection with or without symptoms in Bangladesh (n = 116) *This is a preliminary report that has not yet been peer reviewed.*	**Key Inclusion Criteria:** • Laboratory-confirmed SARS-CoV-2 infection by RT-PCR • SpO_2 ≥95% • Normal or near-normal CXR • No unstable comorbidities **Interventions** *Group A:* • A single dose of IVM 200 µg/kg plus DOX 100 mg twice daily for 10 days	**Number of Participants:** • Group A (n = 60) and Group B (n = 56) **Participant Characteristics:** • Mean age was 33.9 years. • 72% of participants were male. • 91 of 116 participants (78.5%) were symptomatic. **Outcomes:** • In Group A, PCR became negative in 60 of 60 patients (100%). Mean time to negative PCR result was 8.93 days (range 8–13 days).	**Limitations:** • Small sample size • Open-label study • No SOC alone group • Study enrolled young patients without major risk factors for disease progression. • None of the comparative outcome measures were statistically significant.

Study Design	Methods	Results	Limitations and Interpretation
Ivermectin Plus Doxycycline Versus Hydroxychloroquine Plus Azithromycin for Asymptomatic Patients and Patients with Mild to Moderate COVID-19[3], continued			
	Group B: • HCQ 400 mg on Day 1, then HCQ 200 mg twice daily for 9 days plus AZM 500 mg once daily for 5 days **Primary Endpoints:** • Time to negative PCR result. Asymptomatic patients were tested starting on Day 5, then every other day until a negative result occurred. Symptomatic patients were tested on their second symptom-free day, then every other day until a negative result occurred. • Time to resolution of symptoms	• In Group B, PCR became negative in 54 of 56 patients (96.4%). Mean time to negative PCR result was 9.33 days (range 5–15 days). • Difference between groups in time from recovery to negative PCR result was not statistically significant ($P = 0.2314$). • In a subgroup analysis of patients who were symptomatic at baseline, the mean durations to negative PCR for Groups A and B were 9.06 days and 9.74 days, respectively ($P = 0.0714$). • In the subgroup analysis, the mean symptom recovery durations for Groups A and B were 5.93 days (range 5–10 days) and 6.99 days (range 4–12 days), respectively ($P = 0.071$). • Patients receiving IVM plus DOX had fewer AEs than those receiving HCQ plus AZM (31.7% vs. 46.4%) in the subgroup analysis.	**Interpretation:** • In this small study with a young population, the authors suggested that IVM plus DOX was superior to HCQ plus AZM despite no statistically significant difference in time from recovery to negative PCR result and symptom recovery between patients who received IVM plus DOX and those who received HCQ plus AZM.
Effect of Early Treatment With Ivermectin Versus Placebo on Viral Load, Symptoms, and Humoral Response in Patients With Mild COVID-19[4]			
A single-center, randomized, double-blind, placebo-controlled pilot trial in Spain (n = 24)	**Key Inclusion Criteria:** • Laboratory-confirmed SARS-CoV-2 infection • ≤72 hours of symptoms • No risk factors for severe disease or COVID-19 pneumonia **Interventions:** • Single dose of IVM 400 µg/kg • Nonmatching placebo tablet administered by a nurse who did not participate in the patient's care **Primary Endpoint:** • Positive SARS-CoV-2 PCR result from an NP swab at Day 7 post-treatment	**Number of Participants:** • IVM (n = 12) and placebo (n = 12) **Participant Characteristics:** • Mean age was 26 years (range 18–54 years). • 50% of participants were male. • All participants had symptoms at baseline; 70% had headache, 66% had fever, 58% had malaise, and 25% had cough. • Median onset of symptoms was 24 hours in IVM arm and 48 hours in placebo arm. **Outcomes:** • At Day 7, 12 patients (100%) in both groups had a positive PCR (for gene N), and 11 of 12 who received IVM (92%) and 12 of 12 who received placebo (100%) had a positive PCR (for gene E); $P = 1.0$ for both comparisons. • In a post hoc analysis, the authors reported fewer patient-days of cough and anosmia in the IVM-treated patients, but no differences in the patient-days for fever, general malaise, headache, and nasal congestion.	**Limitations:** • Small sample size • PCR is not a validated surrogate marker for clinical efficacy. • PCR cycle threshold values were higher for patients who received IVM than those who received placebo at some time points, but these comparisons are not statistically significant. • Symptom results were not a prespecified outcome and are of unclear statistical and clinical significance. **Interpretation:** • Patients who received IVM showed no difference in viral clearance compared to those who received placebo.

Study Design	Methods	Results	Limitations and Interpretation
Effect of Early Treatment With Ivermectin Versus Placebo on Viral Load, Symptoms, and Humoral Response in Patients With Mild COVID-19[4], continued			
			• The small sample size and large number of comparisons make it difficult to assess the clinical efficacy of IVM in this population.
Ivermectin Plus Doxycycline Plus Standard Therapy Versus Standard Therapy Alone in Patients With Mild to Moderate COVID-19[5]			
Randomized, unblinded, single-center study of patients with laboratory-confirmed SARS-CoV-2 infection in Baghdad, Iran (n = 140) *This is a preliminary report that has not yet been peer reviewed.*	**Key Inclusion Criteria:** • Diagnosis by clinical, radiological, and PCR testing • Outpatients had mild or moderate COVID-19, while inpatients had severe and critical COVID-19. **Interventions:** • IVM 200 µg/kg PO daily for 2 days. If patient required more time to recover, a third dose was given 7 days after the first dose, plus DOX 100 mg twice daily for 5–10 days plus standard therapy (based on clinical condition). • Standard therapy was based on clinical condition and included AZM, acetaminophen, vitamin C, zinc, vitamin D3, dexamethasone 6 mg daily or methylprednisolone 40 mg twice daily if needed, and oxygen or mechanical ventilation if needed. • All critically ill patients were assigned to receive IVM plus DOX.	**Number of Participants:** • IVM plus DOX plus standard therapy (n = 70) and standard therapy alone (n = 70) **Participant Characteristics:** • Median age was 50 years in IVM arm and 47 years in standard therapy arm. • 50% of patients were male in IVM arm and 53% were male in standard therapy arm. • In IVM arm, 48 patients had mild or moderate COVID-19, 11 had severe COVID-19, and 11 had critical COVID-19. • In standard therapy arm, 48 patients had mild or moderate COVID-19, 22 had severe COVID-19, and no patients had critical COVID-19. **Outcomes:** • Mean recovery time in IVM arm was 10.1 days (SD 5.3 days) vs. 17.9 days (SD 6.8 days) for standard therapy arm ($P < 0.0001$). This result was only significant for those with mild to moderate disease. • Disease progression occurred in 3 of 70 patients (4.3%) in IVM arm and 7 of 70 (10.0%) in standard therapy arm ($P = 0.19$) • 2 of 70 patients (2.85%) in IVM arm and 6 of 70 (8.57%) in standard therapy arm died ($P = 0.14$)	**Limitations:** • Not blinded • Patient deaths prevent an accurate comparison of mean recovery time between arms in this study, and the authors did not account for competing mortality risks. • Relies heavily on post hoc subgroup comparisons. • Substantial imbalance in disease severity at baseline • Authors noted that critical patients were not assigned to standard therapy arm; thus, the arms were not truly randomized. • Unclear how many patients required corticosteroids. **Interpretation:** • IVM may shorten the time to recovery for patients with mild or moderate disease, but the lack of control for competing mortality causes in the study limits the ability to interpret the results.

Study Design	Methods	Results	Limitations and Interpretation
Efficacy and Safety of Ivermectin Versus Hydroxychloroquine for Treatment of COVID-19[6]			
Multicenter RCT that compared the use of IVM and HCQ in patients with mild, moderate, or severe COVID-19 in hospital settings (n = 400) *This is a preliminary report that has not yet been peer reviewed.*	**Key Inclusion Criteria:** • Positive RT-PCR result • Mild, moderate, or severe cases of COVID-19 **Key Exclusion Criteria:** • Contraindications for HCQ • Critical cases of COVID-19 • Chronic kidney, liver, or heart disease **Interventions** *All Patients:* • SOC, which included AZM 500 mg once daily for 6 days, vitamin C 1 gm once daily, zinc 50 mg once daily, lactoferrin 100 mg twice daily, acetylcysteine 200 mg 3 times daily, prophylactic or therapeutic anticoagulation if D-dimer >1,000, and paracetamol as needed. *Group 1 (Mild or Moderate) and Group 3 (Severe):* • IVM 400 µg/kg once daily for 4 days (maximum of IVM 24 mg per day) *Group 2 (Mild or Moderate) and Group 4 (Severe):* • HCQ 400 mg every 12 hours on Day 1, then HCQ 200 mg every 12 hours for 5 days **Primary Endpoints:** • Clinical laboratory improvement and/or 2 consecutive negative PCR results ≥48 hours apart • Length of hospital stay	**Number of Participants:** • All 4 arms (n = 100 in each arm) **Participant Characteristics:** • Mean age was 53.8–59.6 years. • 67% to 72% of patients were male. • Fatigue and dyspnea reported in 36% to 38% of patients with mild or moderate disease and 86% to 88% of those with severe disease. **Primary Outcomes:** • In those with mild or moderate disease, patients who received IVM had significant differences in improvement compared to those who received HCQ (99% vs. 74%), progression of disease (1% vs. 22%), death (0% vs. 4%), and mean number of hospital days (5±1 vs. 15±8) ($P < 0.001$ for all parameters except death). • For those with severe disease, patients who received IVM had significant differences compared to those who received HCQ in improvement (94% vs. 50%), progression of disease (4% vs. 30%), death (2% vs. 20%), and mean number of hospital days (6±8 vs. 18±8) ($P < 0.001$ for all parameters). • For all patients, those treated with IVM had significant improvement in TLC, CRP, ferritin, D-dimer, and RT-PCR conversion days by Week 1 ($P < 0.001$) compared to those who received HCQ. • In addition to the markers listed above, patients with severe disease showed greater improvement in hemoglobin in IVM arm than in HCQ arm.	**Limitations:** • Unclear whether the study team and patients were blinded. • The role of SOC therapy in clinical and laboratory responses is unknown. • Cannot rule out potential harm from HCQ. It is unknown whether using AZM plus HCQ could have led to worse outcomes. • No SOC alone group • Laboratory results are only reported after 1 week of treatment. Length of follow up for clinical outcomes and mortality is unclear. **Interpretation:** • Compared to those who received HCQ, IVM recipients had improved inflammatory markers and time to RT-PCR conversion after 1 week. Improvement in clinical status and decreased mortality was also observed in the IVM arm.

Study Design	Methods	Results	Limitations and Interpretation
Antiviral Effect of High-Dose Ivermectin in Adults with COVID-19[7]			

Multicenter, randomized, open-label, blinded trial of hospitalized adults with mild to moderate COVID-19 (n = 45)
 	
This is a preliminary report that has not yet been peer-reviewed.
	Key Inclusion Criteria:
	• Laboratory-confirmed SARS-CoV-2 infection
	• Hospitalized with WHO Stage 3 to 5 COVID-19
	• ≤5 days of symptoms
	Key Exclusion Criteria:
	• Use of any agent with potential anti-SARS-CoV-2 activity or immunomodulators prior to enrollment
	• Poorly controlled comorbidities
	Interventions:
	• IVM 600 µg/kg once daily plus SOC for 5 days
	• SOC for 5 days
	Primary Endpoint:
	• VL reduction at Day 5. VL was quantified by NP swab at baseline, then at 24, 48, and 72 hours and Day 5.
	PK Sampling:
	• Performed 4 hours after dose on Days 1, 2, 3, 5, and 7 to assess elimination
		Number of Participants:
		• IVM (n = 30) and SOC (n = 15)
		• After excluding patients with poor sample quality, those without a detectable VL at baseline, and those who withdrew, 32 patients (20 IVM, 12 SOC) were included in the viral efficacy analysis population.
		Participant Characteristics:
		• Mean age was 40.9 years ± 12.5 years.
		• 56% of patients were male.
		Primary Outcomes:
		• Nonstatistically significant difference in baseline VL between arms. The baseline median VL was 3.74 $\log_{10}$ copies/mL (range 2.8–5.79) in IVM arm and 5.59 $\log_{10}$ copies/mL in SOC arm ($P = 0.08$).
		• By Day 5, a similar magnitude of viral reduction was seen in both arms.
		Other Outcomes:
		• A significant positive correlation was found after analysis of mean plasma IVM concentration in relation to VL reduction. Participants with higher IVM concentrations had greater reductions in VL (r 0.44; $P < 0.04$). This correlation was stronger when reduction in VL was related to the IVM exposure corrected by baseline VL (r 0.60; $P < 0.004$).
		• Treated patients were divided into 2 groups based on IVM C_{max}: IVM >160 ng/mL (median of 202 ng/mL) and ≤160 ng/mL (median of 109 ng/mL).
		  • Median percentage of VL reduction by C_{max} concentration vs. control ($P = 0.0096$) was 72% (IQR 59% to 77%) in >160 ng/mL group (n = 9), 40% (IQR 21% to 46%) in ≤160 ng/mL group (n = 11), and 42% (IQR 31% to 73%) in SOC arm.
		  • Median viral decay rate ($P = 0.041$) was 0.64 d^{-1} in >160 ng/mL group, 0.14 d^{-1} in ≤160 ng/mL group, and 0.13 d^{-1} in SOC arm.
		• Percentages of AEs were similar between the arms (43% in IVM arm, 33% in SOC arm), and AEs were mostly mild. No correlation was found between IVM concentration and the occurrence of AEs.
			Limitations:
			• Small sample size
			• No clinical response data reported.
			• The C_{max} level of 160 ng/mL used in the analysis appears to be arbitrary.
			Interpretation:
			• Concentration-dependent virologic response was seen using a higher-than-usual dose of IVM (600 µg/kg vs. 200 or 400 µg/kg once daily), with minimal associated toxicities.
			• The study results showed large interpatient variation of IVM C_{max}. Larger sample sizes are needed to further assess the safety and efficacy of using higher doses of IVM to treat COVID-19.

Study Design	Methods	Results	Limitations and Interpretation
Ivermectin as Adjunctive Therapy to Hospitalized Patients With COVID-19[8]			

Randomized, double-blind, placebo-controlled multicenter Phase 2 clinical trial of hospitalized adults with mild to severe SARS-CoV-2 infection in 5 facilities in Iran (n = 180)
This is a preliminary report that has not yet been peer-reviewed.
	Key Inclusion Criteria:
	• Symptoms suggestive of COVID-19 pneumonia, with chest CT compatible with mild to severe COVID-19 or positive RT-PCR result for SARS-CoV-2
	Key Exclusion Criteria:
	• Severe immunosuppression, malignancy, or chronic kidney disease
	• Pregnancy
	Interventions:
	• HCQ 200 mg/kg twice daily alone as SOC (standard arm)
	• SOC plus 1 of the following:
	  • Placebo
	  • Single dose of IVM 200 µg/kg
	  • IVM 200 µg/kg on Days 1, 3, and 5
	  • Single dose of IVM 400 µg/kg
	  • IVM 400 µg/kg on Day 1, then IVM 200 µg/kg on Days 3 and 5
	Primary Endpoint:
	• Clinical recovery within 45 days of enrollment (defined as normal temp, respiratory rate, and SpO_2 >94% for 24 hours)
		Number of Participants:
		• All 6 arms (n = 30 in each arm)
		Participant Characteristics:
		• Average age was 56 years (range 45–67 years).
		• 50% of patients were male.
		• Disease stratification (based on CT findings): negative (1%), mild (14%), moderate (73%), and severe (12%)
		• Mean SpO_2 at baseline was 89%.
		Primary Outcomes:
		• Durations of hypoxemia ($P = 0.025$) and hospitalization ($P = 0.006$) were shorter in the IVM arms compared to placebo arm, and mortality was lower in the IVM arms ($P = 0.001$).
		• There was no difference in number of days of tachypnea ($P = 0.584$) or return to normal temperature ($P = 0.102$).
		• Significant differences in change from baseline to Day 5 in absolute lymphocyte count, platelet count, erythrocyte sedimentation rate, and CRP.
		• Higher mortality was reported in standard and placebo arm than IVM arms.
			Limitations:
			• Small study
			• Power estimation is confusing.
			• Mortality was not listed as the primary or secondary outcome.
			• It is unclear whether IVM patients also received HCQ.
			• It is unclear whether the between-group comparisons are between combined IVM group and placebo plus SOC.
			• Participants were stratified by disease severity based on CT findings. These categorizations are unclear and were not taken into account in outcome comparisons.
			• The post hoc grouping of randomized arms raises risk of false positive findings.
			Interpretation:
			• IVM appeared to improve laboratory outcomes and some clinical outcomes (shorter duration of hypoxemia and hospitalization) and lowered mortality.
			• The small size of the study, the unclear treatment arm assignments, and the lack of accounting of disease severity at baseline make it difficult to draw conclusions about the efficacy of using IVM to treat patients with mild COVID-19.

Study Design	Methods	Results	Limitations and Interpretation
Retrospective Analysis of Ivermectin in Hospitalized Patients With COVID-19[9]			
Retrospective analysis of consecutive patients with laboratory-confirmed SARS-CoV-2 infection who were admitted to 4 Florida hospitals (n = 276)	**Key Inclusion Criteria:** • Positive NP swab with SARS-CoV-2 RNA **Interventions:** • Single dose of IVM 200 µg/kg, repeated on Day 7 at the doctors' discretion; 90% percent of patients also received HCQ. • Usual care: 97% of patients received HCQ and most also received AZM. **Primary Endpoint:** • All-cause, in-hospital mortality	**Number of Participants:** • IVM (n = 173; 160 participants received a single dose, 13 participants received a second dose) and usual care (n = 103) **Participant Characteristics:** • Mean age was 60.2 years in IVM arm and 58.6 years in the usual care arm. • 51.4% of patients were male in IVM arm and 58.8% were male in usual care arm. • 56.6% of patients were Black in IVM arm and 51.4% were Black in usual care arm. **Outcomes:** • All-cause mortality was lower in IVM arm than in usual care arm (OR 0.27; 95% CI, 0.09–0.80; $P = 0.03$); the benefit appeared to be limited to the subgroup of patients with severe disease. • No difference in median length of hospital stay between arms (7 days for both) or proportion of mechanically ventilated patients who were successfully extubated (36% in IVM arm vs. 15% in usual care arm; $P = 0.07$).	**Limitations:** • Not randomized • Little to no information on oxygen saturation or radiographic findings • Timing of therapeutic interventions was not standardized. • Ventilation and hospitalization duration analyses do not appear to account for death as a competing risk. • No virologic assessments were performed. **Interpretation:** • IVM use was associated with lower mortality than usual care. However, the limitations of this retrospective analysis make it difficult to draw conclusions about the efficacy of using IVM to treat patients with COVID-19.

Study Design	Methods	Results	Limitations and Interpretation
Observational Study on the Effectiveness of Hydroxychloroquine, Azithromycin, and Ivermectin Among Hospitalized Patients With COVID-19[10]			

Retrospective cohort study of hospitalized adults with COVID-19 in Peru (n = 5,683)
This is a preliminary report that has not yet been peer-reviewed.
	Key Inclusion Criteria:
	• Aged ≥18 years
	• Symptomatic
	• Laboratory-confirmed SARS-CoV-2 infection
	• No life-threatening illness at admission
	Key Exclusion Criteria:
	• Required oxygen at admission
	• Use of tocilizumab, LPV/RTV, or RDV
	Interventions:
	• One of the following interventions administered within 48 hours of admission:
	  • HCQ or CQ alone
	  • IVM alone
	  • AZM alone
	  • HCQ or CQ plus AZM
	  • IVM plus AZM
	  • SOC (e.g., supportive care, antipyretics, hydration)
	Primary Endpoint:
	• All-cause mortality
	Secondary Endpoint:
	• All-cause mortality and/or transfer to ICU
		Number of Participants:
		• HCQ or CQ alone (n = 200), IVM alone (n = 203), AZM alone (n = 1,600), HCQ or CQ plus AZM (n = 692), IVM plus AZM (n = 358), and SOC (n = 2,630)
		Participant Characteristics:
		• 63% of patients were male.
		• Mean age was 59.4 years (range 18–104 years).
		• All patients had mild or moderate disease.
		Outcomes:
		• Median follow-up time was 7 days. Mortality rate was 18.9% at the end of follow up.
		• IVM alone was associated with increased risk of death and/or ICU transfer compared to SOC (wHR 1.58; 95% CI, 1.11–2.25).
		• IVM plus AZM did not have an effect on deaths or any secondary outcomes (all-cause death and/or ICU transfer, all-cause death and/or oxygen prescription) compared to SOC.
		• HCQ or CQ plus AZM was associated with a higher risk of death (wHR 1.84; 95% CI, 1.12–3.02), death and/or ICU transfer (wHR 1.49; 95% CI, 1.01–2.19), and death and/or oxygen prescription (wHR 1.70; 95% CI, 1.07–2.69) compared to SOC.
			Limitations:
			• Not randomized
			• Unclear whether all patients received IVM or other medications according to Peruvian guidelines referred to in the manuscript.
			• Dosing and timing of administration are unclear.
			Interpretation:
			• Compared to SOC, IVM alone was associated with increased risk of death and/or ICU admission. Using IVM in combination with AZM was not associated with effects on mortality, ICU transfer, or oxygen prescription compared to SOC.

Study Design	Methods	Results	Limitations and Interpretation
Retrospective Study of Ivermectin Versus Standard of Care in Patients With COVID-19[11]			
Retrospective study of consecutive adult patients hospitalized in Bangladesh with laboratory-confirmed SARS-CoV-2 infection (n = 248)	**Key Inclusion Criteria:** • Aged ≥18 years • Positive NP swab with SARS-CoV-2 RNA • "Free from any other serious pathological conditions" **Interventions:** • Single dose of IVM 12 mg within 24 hours of hospital admission • SOC **Primary Outcome:** • Not specified	**Number of Participants:** • IVM (n = 115) and SOC (n = 133) **Participant Characteristics:** • Median age in IVM arm was 34 years; 70% of participants were male. • Median age in SOC arm was 35 years; 52% of participants were male. • All participants had mild or moderate disease. • 12% of participants had hypertension in both arms. • 17% of participants in IVM arm and 12% in SOC arm had diabetes mellitus. **Outcomes:** • Fewer patients in IVM arm had evidence of disease progression compared to SOC arm ($P < 0.001$): moderate respiratory distress (2.6% vs. 15.8%), pneumonia (0% vs. 9.8%), ischemic stroke (0% vs. 1.5%). • Fewer patients in IVM arm required intensive care management compared to SOC arm (0.9% vs. 8.8%; $P < 0.001$). • Fewer patients in IVM arm required antibiotic therapy (15.7% vs. 60.2%; $P < 0.001$) or supplemental oxygen (9.6% vs. 45.9%; $P < 0.001$) compared to SOC arm. • Shorter median duration of viral clearance in IVM arm compared to SOC arm (4 vs. 15 days; $P < 0.001$). • Shorter median duration of hospital stay in IVM arm compared to SOC arm (9 vs. 15 days; $P < 0.001$) • Lower mortality in IVM arm compared to SOC arm (0.9% vs. 6.8%; $P < 0.05$)	**Limitations:** • Not randomized • Disease severity at admission was reported as mild or moderate, but 12% of patients in IVM arm and 9% in SOC arm had SpO_2 <94% • Even though only 10% of patients developed pneumonia, 60% received antibiotics. • Possibility of harm from concomitant medications **Interpretation:** • Compared to SOC, IVM use was associated with faster rates of viral clearance and better clinical outcomes, including shorter hospital stay and lower mortality

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

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Lopinavir/Ritonavir and Other HIV Protease Inhibitors

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

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

Recommendations

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

Rationale

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

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

Adverse Events

The adverse events for lopinavir/ritonavir include:

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

Drug-Drug Interactions

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

Considerations in Pregnancy

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

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

Considerations in Children

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

Summary of Clinical Data for COVID-19

- The plasma drug concentrations achieved using typical doses of lopinavir/ritonavir are far below the levels that may be needed to inhibit SARS-CoV-2 replication.[3]
- Lopinavir/ritonavir did not demonstrate a clinical benefit in hospitalized patients with COVID-19 during a large randomized trial in the United Kingdom.[4]
- In a large international randomized trial, lopinavir/ritonavir did not reduce the mortality rate among hospitalized patients with COVID-19.[5]
- A moderately sized randomized trial (n = 199) failed to find a virologic or clinical benefit of lopinavir/ritonavir over standard of care.[6]
- Results from a small randomized controlled trial showed that darunavir/cobicistat was not effective for the treatment of COVID-19.[7]
- There are no data from clinical trials that support using other HIV protease inhibitors to treat COVID-19.
- Please see Clinical Data for COVID-19 below for more information.

Clinical Data for COVID-19

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

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

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

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

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

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

Patient Characteristics

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

Results

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

Limitations

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

Interpretation

Lopinavir/ritonavir did not decrease 28-day all-cause mortality when compared to the usual standard of care in hospitalized persons with clinically suspected or laboratory-confirmed SARS-CoV-2 infection. Participants who received lopinavir/ritonavir and those who received standard of care only had similar median lengths of hospital stay. Among the patients who were not on invasive mechanical ventilation at

the time of randomization, those who received lopinavir/ritonavir were as likely to require intubation or die during hospitalization as those who received standard of care.

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

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

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

Patient Characteristics

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

Results

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

Limitations

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

Interpretation

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

Lopinavir/Ritonavir Pharmacokinetics in Patients With COVID-19

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

chromatography-tandem mass spectrometry.[3]

Results

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

Limitations

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

Interpretation

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

Other Reviewed Studies

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

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

Last Updated: February 11, 2021

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

Dosing Regimens *The doses listed here are for approved indications or from reported experiences or clinical trials.*	**Adverse Events**	**Monitoring Parameters**	**Drug-Drug Interaction Potential**	**Panel's Recommendations, Comments, and Links to Clinical Trials**
Chloroquine				
Dose Previously Suggested in an EUA for Adults and Adolescents Weighing ≥50 kg: • 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 • GI 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 **(AIIa)**. • The Panel **recommends against** the use of high-dose CQ (600 mg twice daily for 10 days) for the treatment of COVID-19 **(AI)**. • Dose-dependent toxicity • A list of clinical trials is available here: Chloroquine

Dosing Regimens *The doses listed here are for approved indications or from reported experiences or clinical trials.*	**Adverse Events**	**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]			
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 • GI effects (e.g., nausea, vomiting, diarrhea) • Hepatitis • Hypoglycemia • Myopathy • Anxiety, agitation, hallucinations, psychosis • Allergic reaction/rash • Given the risk of heart rhythm problems, the FDA cautions against using HCQ to treat COVID-19 outside of a hospital or a clinical trial.[1]	• 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 **recommends against** the use of HCQ with or without AZM for the treatment of COVID-19, except in a clinical trial **(AIIa)**. • Long elimination; half-life is 40–55 days. • Dose-dependent toxicity • A list of clinical trials is available here: Hydroxychloroquine

Dosing Regimens *The doses listed here are for approved indications or from reported experiences or clinical trials.*	**Adverse Events**	**Monitoring Parameters**	**Drug-Drug Interaction Potential**	**Panel's Recommendations, Comments, and Links to Clinical Trials**
Ivermectin				
Adults: • The dose most commonly used in clinical trials is IVM 0.2–0.6 mg/kg given as a single dose or as a once-daily dose for up to 5 days.	• Generally well tolerated • Dizziness • Pruritis • GI effects (e.g., nausea, diarrhea) • Neurological AEs have been reported with the use of IVM for the treatment of parasitic diseases, but it is not clear whether these AEs were caused by IVM or the underlying conditions.	• Monitor for potential AEs.	• Minor CYP3A4 substrate • P-gp substrate	• There are insufficient data for the Panel to recommend either for or against the use of IVM for the treatment of COVID-19. • Generally given on an empty stomach with water; however, administering IVM with food increases its bioavailability.[2] • A list of clinical trials is available here: Ivermectin
Lopinavir/Ritonavir				
Adults: • 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	• GI 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 is given with other QTc-prolonging medications.	**High Drug-Drug Interaction Potential** *Lopinavir:* • CYP3A4 inhibitor and substrate *Ritonavir:* • CYP3A4 > CYP2D6 substrate • Potent CYP3A4 and CYP2D6 inhibitor • Inducer of UGT1A1 and CYP1A2, CYP2C8, CYP2C9, and CYP2C19	• The Panel **recommends against** the use of LPV/RTV for the treatment of COVID-19 in hospitalized patients **(AI)**. • The Panel **recommends against** the use of LPV/RTV for the treatment of COVID-19 in nonhospitalized patients **(AIII)**. • Liquid formulation is commercially available. Crushing LPV/RTV tablets may result in significantly decreased drug exposure (AUC ↓ 45%).[3] • Use with caution in patients with hepatic impairment. • A list of clinical trials is available here: Lopinavir/Ritonavir
Remdesivir				
For Hospitalized Adult and Pediatric Patients (Aged ≥12 Years and Weighing ≥40 kg)	• Nausea • ALT and AST elevations • Hypersensitivity	• Infusion reactions • Renal function, hepatic function,	• Clinical drug-drug interaction studies of RDV have not been conducted.	• See Therapeutic Management of Patients with COVID-19 for recommendations on using RDV with or without dexamethasone.

Dosing Regimens *The doses listed here are for approved indications or from reported experiences or clinical trials.*	**Adverse Events**	**Monitoring Parameters**	**Drug-Drug Interaction Potential**	**Panel's Recommendations, Comments, and Links to Clinical Trials**
Remdesivir, continued				
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 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.	• Nausea • ALT and AST elevations • Hypersensitivity • Increases in prothrombin time • Drug vehicle is SBECD, which has been associated with renal toxicity. SBECD accumulation may occur in patients with moderate or severe renal impairment. • Each 100 mg vial of RDV lyophilized powder contains 3 g of SBECD and each 100 mg/20 mL vial of RDV solution contains 6 g of SBECD.	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.[4]	• In vitro, RDV is a substrate of CYP3A4, OATP1B1, and P-gp and an inhibitor of CYP3A4, OATP1B1, OATP1B3, and MATE1.[4] • Minimal to no reduction in RDV exposure is expected when RDV is coadministered with dexamethasone (Gilead Sciences, written communication, July 2020). • CQ or HCQ may decrease the antiviral activity of RDV; coadministration of these drugs **is not recommended**.[4] • No significant interaction is expected between RDV and oseltamivir or baloxavir (Gilead Sciences, personal and written communications, August and September 2020).	• 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

Dosing Regimens *The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Remdesivir, continued				
• 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				

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

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

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Anti-SARS-CoV-2 Antibody Products

Last Updated: February 11, 2021

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 products for the treatment of COVID-19:
  • COVID-19 convalescent plasma
  • The Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the use of convalescent plasma for hospitalized patients with COVID-19 (see Convalescent Plasma for more details).
  • Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunoglobulins
• There are currently insufficient data for the Panel to recommend either for or against the use of the following anti-SARS-CoV-2 monoclonal antibodies for the treatment of nonhospitalized patients with mild to moderate COVID-19:
  • Bamlanivimab
  • The combination of casirivimab plus imdevimab
  • The FDA has issued EUAs for the use of bamlanivimab and the casirivimab plus imdevimab combination for nonhospitalized patients with mild to moderate COVID-19 who are at high risk of disease progression (see Anti-SARS-CoV-2 Monoclonal Antibodies for more details).
• The FDA also recently issued an EUA for bamlanivimab plus etesevimab for the treatment of certain nonhospitalized patients with mild to moderate COVID-19; the Panel will issue recommendations on the use of this combination shortly.

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

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.

Anti-SARS-CoV-2 Monoclonal Antibodies

Last Updated: February 11, 2021

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

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

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

Background

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

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

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

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

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

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

Clinical Trial Data to Date

Bamlanivimab

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

Casirivimab Plus Imdevimab

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

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

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

Please see Table 3a for additional information.

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

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

Rationale for the Panel's Recommendations

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

Please see Table 3a for additional information.

Monitoring

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

Adverse Effects

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

Drug-Drug Interactions

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

Considerations in Pregnancy

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

Considerations in Children

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

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

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

Clinical Trials

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

Drug Availability

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

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

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

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

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

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

Last Updated: February 11, 2021

Study Design	Methods	Results	Limitations and Interpretation
LY-CoV555 (Bamlanivimab) in Outpatients with COVID-19 (BLAZE-1 Interim Analysis)[1]			

Double-blind, placebo-controlled, Phase 2 randomized trial in outpatients with mild to moderate COVID-19 (n = 452)	**Key Inclusion Criteria:**
	• Aged ≥18 years
	• Not currently hospitalized
	• ≥1 mild or moderate COVID-19 symptom
	Key Exclusion Criteria:
	• SpO_2 ≤93% on room air, *or*
	• Respiratory rate ≥30 breaths/min, *or*
	• Heart rate ≥125 bpm
	Interventions:
	• Single IV infusion of:
	  • BAM 700 mg, *or*
	  • BAM 2,800 mg, *or*
	  • BAM 7,000 mg
	• Placebo
	• Administered within 3 days after a positive SARS-CoV-2 virologic test result
	Primary Endpoint:
	• Mean decrease in NP SARS-CoV-2 VL from baseline to Day 11 (plus or minus 4 days)
	Secondary Endpoints:
	• COVID-19-related hospitalization, ED visit, or death within 28 days of treatment
	• Safety
	• Symptom burden
		Number of Participants:
		• BAM (n = 309):
		  • BAM 700 mg (n = 101)
		  • BAM 2,800 mg (n = 107)
		  • BAM 7,000 mg (n = 101)
		• Placebo (n = 143)
		Participant Characteristics:
		• Median age: 45 years in combined BAM arms (range: 18–86 years) vs. 46 years in placebo arm (range: 18–77 years)
		• Percentage of participants with risk factors for severe COVID-19: 69.6% in combined BAM arms vs. 66.4% in placebo arm
		• Percentage of participants aged ≥65 years: 10.7% in combined BAM arms vs. 14.0% in placebo arm
		• Median time from symptom onset to infusion of BAM or placebo: 4 days
		Primary Outcomes:
		• The mean log change in NP SARS-CoV-2 VL from baseline to Day 11 was significantly greater among participants in the BAM 2,800 mg arm than among those in the placebo arm: -0.53 (95% CI, -0.98 to -0.08; $P = 0.02$)
		• The decline in VL was not significantly different between the BAM 700 mg and BAM 7,000 mg arms and the placebo arm.
		Secondary Outcomes:
		• The number and percentage of participants with COVID-19-related hospitalizations or ED visits within 28 days of treatment was lower among the
			Limitations:
			• Relatively small number of participants in each arm
			• Low number of hospitalizations or ED visits
			• NP RT-PCR not a validated surrogate marker of disease progression or recovery
			• Interim analysis
			Interpretation:
			• Compared to placebo, a single infusion of BAM 2,800 mg hastened decline of VL at Day 11 among outpatients with mild or moderate COVID-19. This treatment effect was not statistically significant for the other BAM doses.
			• The clinical meaningfulness of this reduction in VL is unclear.
			• The combined hospitalization or emergency visit rate was lower in the BAM arms than in the placebo arm, but the number of events in each arm was small. Similar rates were seen for all 3 BAM doses.
			• Because of the small number of clinical events, it is difficult to draw definitive conclusions about the clinical benefit of BAM; data from larger clinical trials are needed.

Study Design	Methods	Results	Limitations and Interpretation
LY-CoV555 (Bamlanivimab) in Outpatients with COVID-19 (BLAZE-1 Interim Analysis)[1], continued			
		BAM recipients than the placebo recipients: • All BAM doses: 5 of 309 (1.6%) • BAM 700 mg: 1 of 101 (1.0%) • BAM 2,800 mg: 2 of 107 (1.9%) • BAM 7,000 mg: 2 of 101 (2.0%) • Placebo: 9 of 143 (6.3%) • No deaths reported. • In post hoc analysis of high-risk participants (defined as aged ≥65 years or BMI ≥35), number and percentage of participants who required hospitalization or ED visit: • 4 of 95 (4.2%) in combined BAM arms • 7 of 48 (14.6%) in placebo arm • The change in symptom scores (i.e., improvement from baseline) was slightly better among the BAM recipients than among the placebo recipients. • In the BAM arms, there were no SAEs, and the safety profile of BAM was similar to that of the placebo.	
LY-CoV555 (Bamlanivimab) in Hospitalized Patients with COVID-19 (ACTIV-3/TICO Preliminary Report)[2]			
Double-blind, placebo-controlled, randomized trial; a substudy of ACTIV-3/TICO in hospitalized patients with COVID-19 (n = 326)	**Key Inclusion Criteria:** • Adult hospitalized patients • Documented SARS-CoV-2 infection • Duration of COVID-19 symptoms ≤12 days **Key Exclusion Criteria:** • End-organ failure **Interventions:** • Single infusion of BAM 7,000 mg • Placebo	**Number of Participants:** • mITT analysis (n = 314): BAM 7,000 mg (n = 163) and placebo (n = 151) **Participant Characteristics:** • Median age: 63 years (range: 50–72 years) in BAM arm vs. 59 years (range: 48–71 years) in placebo arm • Percentage of participants with coexisting illness: 72% in BAM arm vs. 68% in placebo arm • Median days since symptom onset: 7 days (range: 5–9 days) in BAM arm vs. 8 days (range: 5–9 days) in placebo arm	**Limitations:** • Enrollment was stopped after futility criteria were met, resulting in smaller sample size and limited follow-up period. • Preliminary report **Interpretation:** • No clinical benefit of BAM in hospitalized patients with COVID-19

Study Design	Methods	Results	Limitations and Interpretation
LY-CoV555 (Bamlanivimab) in Hospitalized Patients with COVID-19 (ACTIV-3/TICO Preliminary Report)[2], continued			

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

Study Design	Methods	Results	Limitations and Interpretation
REGN10933 and REGN10987 (Casirivimab Plus Imdevimab) in Outpatients with COVID-19 (R10933-10987-COV-2067)[3]			

Double-blind, placebo-controlled, Phase 1 and 2 randomized trial in outpatients with mild to moderate COVID-19 (n = 799)
 	
Note: These data are from the FDA EUA for CAS plus IMD.
	Key Inclusion Criteria:
	• Onset of COVID-19 symptoms ≤7 days before randomization
	• SpO_2 ≥93% on room air
	Key Exclusion Criteria:
	• Hospitalization before or at randomization due to COVID-19
	• Prior, current, or planned future use of any of the treatments specified in the protocol (e.g., COVID-19 convalescent plasma, IVIG for any indication)
	Interventions:
	• Single IV infusion of CAS plus IMD combination:
	  • CAS plus IMD 2,400 mg (CAS 1,200 mg and IMD 1,200 mg), *or*
	  • CAS plus IMD 8,000 mg (CAS 4,000 mg and IMD 4,000 mg)
	• Placebo
	• Administered ≤3 days after a positive SARS-CoV-2 virologic test result
	Primary Endpoint:
	• TWA change in NP VL from baseline to Day 7
	Secondary Endpoints:
	• COVID-19-related medical visits including hospitalization or ED, urgent care, or physician office/telemedicine visits within 28 days of treatment
	• Safety
	• Symptom improvement
		Number of Participants:
		• CAS plus IMD (n = 533):
		  • CAS plus IMD 2,400 mg (n = 266)
		  • CAS plus IMD 8,000 mg (n = 267)
		• Placebo (n = 266)
		Participant Characteristics:
		• Median age: 42 years (7% aged ≥65 years)
		• Percentage of participants with risk factors for severe COVID-19: 34%
		• Median duration of symptoms: 3 days
		Primary Outcomes:
		• Evaluated in the modified full analysis set of participants with detectable virus at baseline (n = 665)
		• TWA change in NP VL at Day 7 was greater among the CAS plus IMD-treated participants overall than among the placebo-treated participants (-0.36 log_{10} copies/mL; $P < 0.0001$).
		Secondary Outcomes:
		• The proportion of participants who had COVID-19-related medical visits within 28 days of treatment was lower in the combined CAS plus IMD arms than in the placebo arm:
		  • Combined CAS plus IMD arms: 2.8% of patients
		  • Placebo arm: 6.5% of patients
		• In a post hoc analysis, the number and percentage of participants who were hospitalized or had a medical visit within 28 days of treatment:
		  • All CAS plus IMD doses: 8 of 434 (2%)
		  • CAS plus IMD 2,400 mg: 4 of 215 (2%)
		  • CAS plus IMD 8,000 mg: 4 of 219 (2%)
		  • Placebo: 10 of 231 (4%)
			Limitations:
			• Relatively small number of participants in each arm
			• Low number of hospitalizations or ED visits
			• NP RT-PCR is not a validated surrogate marker of disease progression or recovery.
			Interpretation:
			• Compared to placebo, a single infusion of CAS plus IMD showed a reduction in VL at Day 7 among outpatients with mild or moderate COVID-19.
			• The clinical meaningfulness of this reduction in VL is unclear.
			• Combined hospitalization or ED visit rate was lower in CAS plus IMD arms than in the placebo arm, but the number of events in each arm was small.
			• Because of the small number of clinical events, it is difficult to draw definitive conclusions about the clinical benefit of CAS plus IMD; more information is needed.

Study Design	Methods	Results	Limitations and Interpretation
REGN10933 and REGN10987 (Casirivimab Plus Imdevimab) in Outpatients with COVID-19 (R10933-10987-COV-2067)[3], continued			
		• In a post hoc analysis, the number and percentage of participants at high-risk for progression to severe COVID-19 and/or hospitalization who required hospitalization or ED visit: • All CAS plus IMD doses: 4 of 151 (3%) • Placebo: 7 of 78 (9%) • Median time to symptom improvement: • Combined CAS plus IMD arms: 5 days • Placebo arm: 6 days • The safety profile of CAS plus IMD was similar to that of placebo. • 4 infusion related reactions of grade 2 severity or higher were reported in the CAS plus IMD 8,000 mg arm resulting in permanent discontinuation of the infusion in 2 participants; 1 participant had an anaphylactic reaction that resolved with treatment.	
Published Preliminary Subset Analysis of REGN10933 (Casirivimab) Plus REGN10987 (Imdevimab) in Outpatients with COVID-19 (R10933-10987-COV-2067 Interim Analysis)[4] **Note:** The data presented in this interim analysis represent a subset of participants described in the EUA above.			
Double-blind, placebo-controlled, Phase 1 and 2 randomized trial in outpatients with mild to moderate COVID-19 (n = 275)	**Key Inclusion Criteria:** • Onset of COVID-19 symptoms <7 days • SpO_2 ≥93% on room air **Key Exclusion Criteria:** • Hospitalization before or at randomization due to COVID-19 • Prior, current, or planned future use of any of the treatments specified in the protocol (e.g., COVID-19 convalescent plasma, IVIG for any indication)	**Number of Participants:** • All CAS plus IMD doses (n = 182): • CAS plus IMD 2,400 mg (n = 92) • CAS plus IMD 8,000 mg (n = 90) • Placebo (n = 93) **Participant Characteristics:** • Median age: 44 years (range: 35–52 years) • Median time from symptom onset to randomization: 3 days • Baseline serum antibody status: • Positive: 45% of participants • Negative: 41% of participants	**Limitations:** • No formal hypothesis testing • Interim analysis • Relatively small number of participants in each arm • These data represent only a subset of participants described in the EUA (above). • Low number of medical visits • NP RT-PCR is not a validated surrogate marker of disease progression or recovery.

Study Design	Methods	Results	Limitations and Interpretation
Published Preliminary Subset Analysis of REGN10933 (Casirivimab) Plus REGN10987 (Imdevimab) in Outpatients with COVID-19 (R10933-10987-COV-2067 Interim Analysis)[4], continued			

	Interventions:
	• Single IV infusion of CAS plus IMD combination:
	  • CAS plus IMD 2,400 mg (CAS 1,200 mg and IMD 1,200 mg) or
	  • CAS plus IMD 8,000 mg (CAS 4,000 mg and IMD 4,000 mg)
	• Placebo
	• Administered ≤3 days after a positive SARS-CoV-2 virologic test result
	Primary Endpoint:
	• TWA change in NP VL from baseline to Day 7 in participants with negative serum antibody status at baseline
	Secondary Endpoints:
	• COVID-19-related medical visits, including hospitalization or ED, urgent care, or physician office/telemedicine visits within 28 days of treatment
	• Safety
	• Symptom improvement
		• Unknown: 14% of participants
		Primary Outcomes:
		• Evaluated in modified full analysis set of participants with detectable virus at baseline (n = 221)
		• TWA change in NP VL at Day 7 was greater among the participants who received CAS plus IMD (-1.74 ± 0.11 $\log_{10}$ copies/mL; CI, -1.95 to -1.53) than among those who received placebo (-1.34 ± 0.13 $\log_{10}$ copies/mL; CI, -1.60 to -1.08).
		• Among the participants with a negative serum antibody status at baseline, TWA change in VL was greater among those who received CAS plus IMD (-1.94 ± 0.13 $\log_{10}$ copies/mL; CI: -2.20 to -1.67) than among those who received placebo (-1.37 ± 0.20 $\log_{10}$ copies/mL; CI, -1.76 to -0.98).
		Secondary Outcomes:
		• Compared to the placebo participants, the CAS plus IMD participants had fewer COVID-19-related medical visits within 28 days of treatment:
		  • All CAS plus IMD doses: 6 of 182 (3%)
		  • Placebo: 6 of 93 (6%)
		• Among participants with negative serum antibody status at baseline, those who received CAS plus IMD had fewer COVID-19-related medical visits within 28 days of treatment:
		  • All CAS plus IMD doses: 5 of 80 (6%)
		  • Placebo: 5 of 33 (15%)
		• The safety profile of CAS plus IMD was similar to that of the placebo; 2 hypersensitivity or infusion related reactions of grade 2 severity or higher were reported in both the CAS plus IMD 8,000 mg arm and the placebo arm.
		• The mean half-life for both CAS and IMD antibodies ranged from 25–37 days.
			Interpretation:
			• Compared to placebo, a single infusion of CAS plus IMD showed a reduction in VL at Day 7 among outpatients with mild or moderate COVID-19.
			• The clinical meaningfulness of this reduction in VL is unclear.
			• The percentage of participants with medical visits was lower in the CAS plus IMD arms than in the placebo arm, but the number of events in each arm was small.
			• CAS plus IMD may have a greater effect in patients with a negative serum antibody status but further investigation is needed.
			• Because of the small number of clinical events, it is difficult to draw definitive conclusions about the clinical benefit of CAS plus IMD; more information is needed.

Key: AE = adverse event; BAM = bamlanivimab; BMI = body mass index; CAS = casirivimab; EUA = Emergency Use Authorization; ED = emergency department; IMD = imdevimab; IV = intravenous; IVIG = intravenous immunoglobulin; mITT = modified intention to treat; NP = nasopharyngeal; RDV = remdesivir; RT-PCR = reverse transcriptase-polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SpO_2 = saturation of oxygen; TWA = time-weighted average; VL = viral load

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

Last Updated: February 11, 2021

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

Dosing Regimens	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Bamlanivimab (Anti-SARS-CoV-2 Monoclonal Antibody)				
Dose Recommended in an EUA for Nonhospitalized Adult and Pediatric Patients (Aged ≥12 Years and Weighing ≥40 kg) With Mild to Moderate COVID-19 Who are at High Risk for Progressing to Severe COVID-19 and/or Hospitalization: • Single dose of BAM 700 mg IV as soon as possible after a positive result on viral test for SARS-CoV-2 and within 10 days of symptom onset (per EUA)	• Nausea • Diarrhea • Dizziness • Headache • Pruritis • Vomiting • Hypersensitivity, including anaphylaxis and infusion reactions • Unexpected SAEs may occur.	• Only for administration in health care settings by qualified health care providers who have immediate access to medications to treat a severe infusion reaction and emergency medical services. • Monitor patient during the infusion and then observe for ≥1 hour after the infusion is completed.	• Drug-drug interactions are unlikely between BAM and medications that are renally excreted or that are CYP substrates, inhibitors, or inducers.	• To date, there are insufficient data for the Panel to recommend either for or against the use of BAM for the treatment of outpatients with mild to moderate COVID-19. • Patients who are hospitalized for COVID-19 **should not receive** BAM outside of a clinical trial. • A list of clinical trials is available: Bamlanivimab **Availability:** • BAM is available through the FDA EUA for high-risk outpatients with mild to moderate COVID-19.[1] See Anti-SARS-CoV-2 Monoclonal Antibodies for a list of high-risk conditions.

Dosing Regimens	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Casirivimab Plus Imdevimab (Anti-SARS-CoV-2 Monoclonal Antibodies)				
Dose Recommended in an EUA For Nonhospitalized Adult and Pediatric Patients (Aged ≥12 Years and Weighing ≥40 kg) With Mild to Moderate COVID-19 Who are at High Risk for Progressing to Severe COVID-19 and/or Hospitalization: • CAS 1,200 mg and IMD 1,200 mg IV administered together once in a single dose as soon as possible after positive result on viral test for SARS-CoV-2 and within 10 days of symptom onset (per EUA)	• Hypersensitivity, including anaphylaxis and infusion reactions • Unexpected SAEs may occur.	• Only for administration in health care settings by qualified health care providers who have immediate access to medications to treat a severe infusion reaction and emergency medical services. • Monitor patient during the infusion and then observe for at ≥1 hour after the infusion is completed.	• Drug-drug interactions are unlikely between CAS plus IMD and medications that are renally excreted or that are CYP substrates, inhibitors, or inducers.	• To date, there are insufficient data for the Panel to recommend either for or against the use of CAS plus IMD for the treatment of outpatients with mild to moderate COVID-19. • Patients who are hospitalized for COVID-19 **should not receive** CAS plus IMD outside of a clinical trial. • A list of clinical trials is available: Casirivimab plus Imdevimab **Availability:** • CAS plus IMD is available through the FDA EUA for high-risk outpatients with mild to moderate COVID-19.[2] See Anti-SARS-CoV-2 Monoclonal Antibodies for a list of high-risk conditions.
COVID-19 Convalescent Plasma				
1 or more transfusions based on patient response	• TRALI • TACO • Allergic reactions • Anaphylactic reactions • Febrile nonhemolytic reactions • Hemolytic reactions • Hypothermia • Metabolic complications • Transmission of infectious pathogens[3] • Thrombotic events	• Before administering convalescent plasma to patients with a history of severe allergic or anaphylactic transfusion reactions, the Panel recommends consulting a transfusion medicine specialist who is associated with the hospital blood bank. • Monitor for transfusion-related reactions.	• 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: COVID-19 Convalescent Plasma

Dosing Regimens	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
COVID-19 Convalescent Plasma, continued				
	• Theoretical risk of antibody-mediated enhancement of infection and suppressed long-term immunity	• Monitor patient's vital signs at baseline and during and after transfusion.		
SARS-CoV-2 Specific Immunoglobulin				
Dose varies by clinical trial	• TRALI • TACO • Allergic reactions • Antibody-mediated enhancement of infection • Red blood cell alloimmunization • Transmission of infectious pathogens	• Monitor for transfusion-related reactions. • Monitor patient's vital signs at baseline and during and after transfusion.	• Drug products **should not be added** to the IV infusion line for the blood product.	• To date, there are insufficient data for the Panel to recommend either for or against the use of SARS-CoV-2 immunoglobulins for the treatment of COVID-19. • A list of clinical trials is available: SARS-CoV-2 Immunoglobulin

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

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

Last Updated: February 11, 2021

Mesenchymal Stem Cells

Mesenchymal stem cells are investigational products that have been studied extensively for broad clinical applications in regenerative 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 **(AIIb)**.

Rationale for Recommendation

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

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

Rationale for Use in COVID-19

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

Clinical Data

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

Clinical Data for COVID-19

A pilot study of intravenous mesenchymal stem cell transplantation in China enrolled 10 patients with confirmed COVID-19 categorized according to the National Health Commission of China criteria as

critical, severe, or common type. Seven patients (one with critical illness, four with severe illness, and two with common-type illness) received mesenchymal stem cells; three patients with severe illness received placebo. All seven patients who received mesenchymal stem cells recovered. Among the three severely ill placebo-treated patients, one died, one developed acute respiratory distress syndrome (ARDS), and one remained stable with severe disease.[7]

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

Clinical Data for Other Viral Infections

In an open-label study of mesenchymal stem cells for the treatment of H7N9 influenza in China, 17 patients received mesenchymal stem cell treatment plus standard of care, and 44 patients received standard of care only. Three patients (17.6%) in the mesenchymal stem cell group died versus 24 patients (54.5%) in the control group. The 5-year follow-up was limited to five patients in the mesenchymal stem cell group. No safety concerns were identified.[9]

Clinical Trials

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

Adverse Effects

Risks associated with mesenchymal stem cell transfusion appear to be uncommon. The potential risks include failure of the cells to work as expected, potential for mesenchymal stem cells to multiply or change into inappropriate cell types, product contamination, growth of tumors, infections, thrombus formation, and administration site reactions.[10]

Considerations in Pregnancy

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

Considerations in Children

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

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Immunomodulators Under Evaluation for the Treatment of COVID-19

Last Updated: February 11, 2021

Summary Recommendations

See Therapeutic Management of Patients with COVID-19 for the COVID-19 Treatment Guidelines Panel's (the Panel's) recommendations on the use of the following:
• Dexamethasone (or other corticosteroids) with or without remdesivir
• Baricitinib with remdesivir.
 	
See additional recommendations on the use of baricitinib below.
 	
See Statement on the Use of Tocilizumab (and Other Interleukin-6 Inhibitors) for the Panel's recommendations on the use of tocilizumab and sarilumab.
 	
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:
• Baricitinib in combination with corticosteroids. Because both agents are potent immunosuppressants, there is potential for an additive risk of infection.
• Baricitinib in combination with remdesivir for hospitalized COVID-19 patients when corticosteroids can be used
• Interleukin (IL)-1 inhibitors (e.g., anakinra)
• Interferon beta for the treatment of early (i.e., <7 days from symptom onset) mild to moderate COVID-19
 	
The Panel **recommends against** the use of the following immunomodulators for the treatment of COVID-19, except in a clinical trial:
• **Siltuximab**, an anti-IL-6 monoclonal antibody **(AIII)**
• **Baricitinib** without remdesivir **(AIII)**
• **Interferons (alfa or beta)** for the treatment of severely or critically ill patients with COVID-19 **(AIII)**
• Kinase inhibitors:
  • Bruton's tyrosine kinase inhibitors (e.g., **acalabrutinib**, **ibrutinib**, **zanubrutinib**) **(AIII)**
  • Janus kinase inhibitors other than baricitinib (e.g., **ruxolitinib**, **tofacitinib**) **(AIII)**
• **Non-SARS-CoV-2-specific intravenous immune globulin (IVIG) (AIII)**. This recommendation should not preclude the use of IVIG when it is otherwise indicated for the treatment of complications that arise during the course of COVID-19.

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

Corticosteroids

Last Updated: November 3, 2020

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

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

Rationale for Use of Corticosteroids in Patients With COVID-19

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

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

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

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

studies can be found in Table 4a.

Corticosteroids Other Than Dexamethasone

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

Monitoring, Adverse Effects, and Drug-Drug Interactions

- Clinicians should closely monitor patients with COVID-19 who are receiving dexamethasone for adverse effects (e.g., hyperglycemia, secondary infections, psychiatric effects, avascular necrosis).
- Prolonged use of systemic corticosteroids may increase the risk of reactivation of latent infections (e.g., hepatitis B virus [HBV], herpesvirus infections, strongyloidiasis, tuberculosis).
- The risk of reactivation of latent infections for a 10-day course of dexamethasone (6 mg once daily) is not well-defined. When initiating dexamethasone, appropriate screening and treatment to reduce the risk of *Strongyloides* hyperinfection in patients at high risk of strongyloidiasis (e.g., patients from tropical, subtropical, or warm, temperate regions or those engaged in agricultural activities)[22-24] or fulminant reactivations of 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.

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Table 4a. Corticosteroids: Selected Clinical Data

Last Updated: February 11, 2021

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

Study Design	Methods	Results	Limitations and Interpretation
Dexamethasone in Hospitalized Patients With COVID-19—Preliminary Report (RECOVERY Trial)[1]			

Multi-center, randomized open-label adaptive trial in hospitalized patients with suspected or confirmed COVID-19 (n = 6,425)
 	
Country: United Kingdom
	Key Inclusion Criteria:
	• Hospitalization with clinically suspected or laboratory-confirmed SARS-CoV-2 infection
	
	Key Exclusion Criteria:
	• Physician determination that risks of participation too great based on patient's medical history or an indication for corticosteroid therapy outside of the study
	
	Interventions:
	• Patients randomized 2:1 to receive:
	  • Dexamethasone 6 mg PO or IV once daily plus SOC for up to 10 days or until hospital discharge, whichever came first, *or*
	  • SOC alone
	
	Primary Endpoint:
	• All-cause mortality at 28 days after randomization
		Number of Participants:
		• Dexamethasone plus SOC (n = 4,321) and SOC (n = 2,104)
		
		Participant Characteristics:
		• Mean age was 66 years.
		• 64% of participants were men.
		• 56% of participants had ≥1 comorbidity; 24% had diabetes.
		• 89% of participants had laboratory-confirmed SARS-CoV-2 infection.
		• At randomization, 16% of participants received invasive mechanical ventilation or ECMO, 60% required supplemental oxygen but not invasive ventilation, and 24% required no oxygen supplementation.
		• 0% to 3% of the participants in both arms received RDV, HCQ, LPV/RTV, or tocilizumab; approximately 8% of participants in SOC alone arm received dexamethasone after randomization.
		
		Outcomes:
		• 28-day mortality was 22.9% in dexamethasone arm and 25.7% in SOC arm (age-adjusted rate ratio 0.83; 95% CI, 0.75–0.93; $P < 0.001$).
			Limitations:
			• Open label study
			• This preliminary study analysis did not include the results for key secondary endpoints (e.g., cause-specific mortality, need for renal replacement), AEs, and the efficacy of dexamethasone in key subgroups (e.g., patients with comorbidities).
			• Study participants with COVID-19 who required oxygen (but not mechanical ventilation) had variable disease severity; it is unclear whether all patients in this heterogeneous group derived benefit from dexamethasone, or whether benefit is restricted to those requiring higher levels of supplemental oxygen or oxygen delivered through a high-flow device.
			• The age distribution of participants differed by respiratory status at randomization.
			• The survival benefit of dexamethasone for mechanically ventilated patients aged >80 years is unknown because only 1% of the participants in this group were ventilated.

Study Design	Methods	Results	Limitations and Interpretation
Dexamethasone in Hospitalized Patients With COVID-19—Preliminary Report (RECOVERY Trial)[1], continued			
		• The treatment effect of dexamethasone varied by baseline severity of COVID-19. Survival benefit appeared greatest among participants who required invasive mechanical ventilation at randomization. Among these participants, 28-day mortality was 29.3% in dexamethasone arm vs. 41.4% in SOC arm (rate ratio 0.64; 95% CI, 0.51–0.81). • Among patients who required supplemental oxygen but not mechanical ventilation at randomization, 28-day mortality was 23.3% in dexamethasone arm vs. 26.2% in SOC arm (rate ratio 0.82; 95% CI, 0.72–0.94). • No survival benefit in participants who did not require oxygen therapy at enrollment. Among these participants, 28-day mortality was 17.8% in dexamethasone arm vs. 14.0% in SOC arm (rate ratio 1.19; 95% CI, 0.91–1.55).	• It is unclear whether younger patients were more likely to receive mechanical ventilation than patients aged >80 years, given similar disease severity at baseline, with older patients preferentially assigned to oxygen therapy. • The high baseline mortality of this patient population may limit generalizability of the study results to populations with a lower baseline mortality. **Interpretation:** • In hospitalized patients with severe COVID-19 who required oxygen support, using dexamethasone 6 mg daily for up to 10 days reduced mortality at 28 days, with the greatest benefit seen in those who were mechanically ventilated at baseline. • There was no observed survival benefit of dexamethasone in patients who did not require oxygen support at baseline.
Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-Analysis (REACT Working Group)[2]			
Meta-analysis of 7 RCTs of corticosteroids in critically ill patients with COVID-19 (n = 1,703) Countries: Multinational	**Key Inclusion Criteria:** • RCTs evaluating corticosteroids in critically ill patients with COVID-19 (identified via comprehensive search of *ClinicalTrials.gov*, Chinese Clinical Trial Registry, and EU Clinical Trials Register)	**Number of Participants:** • Corticosteroids (n = 678) and usual care or placebo (n = 1,025) **Participant Characteristics:** • Median age was 60 years. • 29% of patients were women. • 1,559 patients (91.5%) were on mechanical ventilation.	**Limitations:** • The design of the trials included in the meta-analysis differed in several ways, including the following: • Definition of critical illness • Specific corticosteroid used • Dose of corticosteroid • Duration of corticosteroid treatment

Study Design	Methods	Results	Limitations and Interpretation
Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-Analysis (REACT Working Group)[2], continued			

	Interventions:
	• Corticosteroids (i.e., dexamethasone, hydrocortisone, methylprednisolone)
	• Usual care or placebo
	Primary Endpoint:
	• All-cause mortality up to 30 days after randomization
		• 47% of patients were on vasoactive agents at randomization across the 6 trials that reported this information.
		Outcomes:
		• Mortality was assessed at 28 days in 5 trials, 21 days in 1 trial, and 30 days in 1 trial.
		• Reported all-cause mortality at 28 days: Death occurred in 222 of 678 patients (32.7%) in corticosteroids group vs. 425 of 1,025 patients (41.5%) in usual care or placebo group; summary OR 0.66 (95% CI, 0.53–0.82; $P < 0.001$).
		• The fixed-effect summary ORs for the association with all-cause mortality were:
		  • Dexamethasone: OR 0.64 (95% CI, 0.50–0.82; $P < 0.001$) in 3 trials with 1,282 patients
		  • Hydrocortisone: OR 0.69 (95% CI, 0.43–1.12; $P = 0.13$) in 3 trials with 374 patients.
		  • Methylprednisolone: OR 0.91 (95% CI, 0.29–2.87; $P = 0.87$) in 1 trial with 47 patients
		  • For patients on mechanical ventilation (n = 1,559): OR 0.69 (95% CI, 0.55–0.86), with mortality of 30% for corticosteroids vs. 38% for usual care or placebo
		  • For patients not on mechanical ventilation (n = 144): OR 0.41 (95% CI, 0.19–0.88) with mortality of 23% for corticosteroids vs. 42% for usual care or placebo
		• Across the 6 trials that reported SAEs, 18.1% of patients randomized to corticosteroids and 23.4% randomized to usual care or placebo experienced SAEs.
			• Type of control group (i.e., usual care or placebo)
			• Reporting of SAEs
			• The RECOVERY trial accounted for 59% of the participants, and 3 trials enrolled <50 patients each.
			• Some studies confirmed SARS-CoV-2 infection for participant inclusion while others enrolled participants with either probable or confirmed infection.
			• Although the risk of bias was low in 6 of the 7 trials, it was assessed as "some concerns" for 1 trial (which contributed only 47 patients).
			Interpretation:
			• Systemic corticosteroids decrease 28-day mortality in critically ill patients with COVID-19 without safety concerns.
			• Most of the participants were from the RECOVERY trial, thus the evidence of benefit in the meta-analysis is strongest for dexamethasone, the corticosteroid used in the RECOVERY trial.

Study Design	Methods	Results	Limitations and Interpretation
Methylprednisolone as Adjunctive Therapy for Patients Hospitalized With COVID-19 (Metcovid): A Randomised, Double-Blind, Phase IIb, Placebo-Controlled Trial[3]			
Randomized, double-blind, placebo-controlled, single-center study of short-course methylprednisolone in hospitalized patients with confirmed or suspected COVID-19 pneumonia (n = 416) Country: Brazil	**Key Inclusion Criteria:** • Aged ≥18 years • Suspected or confirmed COVID-19 • SpO_2 ≤94% on room air *or* while using supplementary oxygen *or* under invasive mechanical ventilation **Key Exclusion Criteria:** • Hypersensitivity to methylprednisolone • Chronic use of corticosteroids or immunosuppressive agents • HIV, decompensated cirrhosis, chronic renal failure **Interventions:** • Methylprednisolone IV 0.5 mg/kg twice daily for 5 days • Placebo (saline) IV **Primary Endpoint:** • Mortality by Day 28 **Secondary Endpoints:** • Early mortality at Days 7 and 14 • Need for mechanical ventilation by Day 7 • Need for insulin by Day 28 • Positive blood culture at Day 7, sepsis by Day 28 • Mortality by Day 28 in specified subgroups	**Number of Participants:** • mITT analysis (n = 393): Methylprednisolone (n = 194) and placebo (n = 199) **Participant Characteristics:** • Mean age was 55 years. • 65% of patients were men. • 29% of patients had diabetes. • At enrollment, 34% of participants in each group required invasive mechanical ventilation; 51% in methylprednisolone group and 45% in placebo group required supplemental oxygen. • Median time from illness onset to randomization was 13 days (IQR 9–16). • None of the participants received anti-IL-6, anti-IL-1, RDV, or convalescent plasma. • Hydrocortisone use for shock among patients was 8.7% in methylprednisolone group and 7.0% in placebo group. **Primary Outcomes:** • No difference in 28-day mortality: 37.1% in methylprednisolone arm vs. 38.2% in placebo arm (HR 0.92; 95% CI, 0.67–1.28; $P = 0.63$). **Secondary Outcomes:** • No difference between groups in early mortality at Day 7 (HR 0.68; 95% CI, 0.43–1.06) or Day 14 (HR 0.82; 95% CI, 0.57–1.18) • No difference in need for mechanical ventilation by Day 7: 19.4% of methylprednisolone recipients vs. 16.8% of placebo recipients ($P = 0.65$)	**Limitations:** • 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:** • Use of weight-based methylprednisolone for 5 days did not reduce overall 28-day mortality. • In a post hoc subgroup analysis, mortality among those aged >60 years was lower in the methylprednisolone group than in the placebo group.

Study Design	Methods	Results	Limitations and Interpretation
Methylprednisolone as Adjunctive Therapy for Patients Hospitalized With COVID-19 (Metcovid): A Randomised, Double-Blind, Phase IIb, Placebo-Controlled Trial[3], continued			
		• No significant difference between the methylprednisolone and placebo groups in need for insulin (59.5% vs. 49.4% of patients), positive blood cultures at Day 7 (8.3% vs. 8.0% of patients), or sepsis by Day 28 (38.1% vs. 38.7% of patients) • In post hoc analysis, 28-day mortality in participants aged >60 years was lower in methylprednisolone group than in placebo group (46.6% vs. 61.9%; HR 0.63; 95% CI, 0.41–0.98).	
Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial[4]			

Multicenter, randomized, clinical trial in patients with COVID-19 and moderate to severe ARDS (n = 299)
Country: Brazil
	Key Inclusion Criteria:
	• Aged ≥18 years
	• Confirmed or suspected COVID-19
	• On mechanical ventilation within 48 hours of meeting criteria for moderate to severe ARDS with PaO_2/FiO_2 ≤200 mm Hg
	Key Exclusion Criteria:
	• Recent corticosteroid use
	• Use of immunosuppressive drugs in the past 21 days
	• Expected death in next 24 hours
	Interventions:
	• Dexamethasone 20 mg IV daily for 5 days, then 10 mg IV daily for 5 days or until ICU discharge plus SOC
	• SOC alone
		Number of Participants:
		• ITT analysis (n = 299): Dexamethasone plus SOC (n = 151) and SOC alone (n = 148)
		Participant Characteristics:
		• Dexamethasone group included more women than the SOC group (40% vs. 35%), more patients with obesity (31% vs. 24%), and fewer patients with diabetes (38% vs. 47%).
		• Other baseline characteristics were similar for the dexamethasone and SOC groups:
		  • Mean age was 60 vs. 63 years; vasopressor use by 66% vs. 68% of patients; mean PaO_2/FiO_2 of 131 mm Hg vs. 133 mm Hg.
		  • Median time from symptom onset to randomization was 9–10 days.
		  • Median time from mechanical ventilation to randomization was 1 day.
		  • No patients received RDV; anti-IL-6 and convalescent plasma were not widely available.
		  • Median duration of dexamethasone therapy was 10 days (IQR 6–10 days).
			Limitations:
			• Open-label study
			• The study was underpowered to assess some outcomes because it stopped enrollment after data from the RECOVERY trial were released.
			• During the study, 35% of the patients in the SOC group received corticosteroids for shock, bronchospasm, or other reasons.
			• Patients who were discharged from the hospital before 28 days were not followed for rehospitalization or mortality.
			• The high baseline mortality of the patient population may limit generalizability of the study results to populations with a lower baseline mortality.
			Interpretation:
			• Compared with SOC alone, dexamethasone at a higher dose than used in the RECOVERY trial plus SOC

Study Design	Methods	Results	Limitations and Interpretation
Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial[4], continued			

	Primary Endpoint:
	• Mean number of days alive and free from mechanical ventilation by Day 28
	Secondary Endpoints:
	• All-cause mortality at Day 28
	• ICU-free days by Day 28
	• Duration of mechanical ventilation by Day 28
	• Score on 6-point WHO ordinal scale at Day 15
	• SOFA score at 7 days
	• Components of the primary outcome or in the outcome of discharged alive within 28 days
		• 35% of patients in SOC alone group also received corticosteroids.
		Primary Outcomes:
		• The mean number of days alive and free from mechanical ventilation by Day 28 was higher in the dexamethasone group than in the SOC group (6.6 vs. 4.0 days, estimated difference of 2.3 days; 95% CI, 0.2–4.4; $P = 0.04$).
		Secondary Outcomes:
		• There were no differences between the dexamethasone and SOC groups for the following outcomes:
		  • All-cause mortality at Day 28 (56.3% vs. 61.5%: HR 0.97; 95% CI, 0.72–1.31; $P = 0.85$)
		  • ICU-free days by Day 28 (mean of 2.1 vs. 2.0 days; $P = 0.50$)
		  • Duration of mechanical ventilation by Day 28 (mean of 12.5 vs.13.9 days; $P = 0.11$)
		  • Score on 6-point WHO ordinal scale at Day 15 (median score of 5 for both groups)
		• The mean SOFA score at 7 days was lower in the dexamethasone group than in the SOC group (6.1 vs. 7.5, difference -1.16; 95% CI, -1.94 to -0.38; $P = 0.004$).
		• The following safety outcomes were comparable for dexamethasone and SOC groups: need for insulin (31.1% vs. 28.4%), new infections (21.9% vs. 29.1%), bacteremia (7.9% vs. 9.5%), and other SAEs (3.3% vs. 6.1%).
		• In post hoc analysis, the dexamethasone group had a lower cumulative probability of death or mechanical ventilation at Day 15 than the SOC group (67.5% vs. 80.4%; OR 0.46; 95% CI, 0.26–0.81; $P = 0.01$).
			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 AEs in this population.
			• More than one-third of those randomized to the standard care alone group also received corticosteroids; it is impossible to determine the effect of corticosteroid use in these patients on the overall study outcomes.

Study Design	Methods	Results	Limitations and Interpretation
Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19: A Randomized Clinical Trial[5]			

Multicenter, randomized, double-blind, sequential trial in patients with confirmed or suspected COVID-19 and acute respiratory failure (n = 149)
 	
Country: France
	Key Inclusion Criteria:
	• Aged ≥18 years
	• Confirmed SARS-CoV-2 infection or radiographically suspected COVID-19, with at least 1 of 4 severity criteria:
	  • Need for mechanical ventilation with PEEP ≥5 cm H_2O
	  • High-flow oxygen with PaO_2/FiO_2 <300 mm Hg and FiO_2 ≥50%
	  • Reservoir mask oxygen with PaO_2/FiO_2 <300 mm Hg (estimated)
	  • Pneumonia severity index >130 (scoring table)
	
	Key Exclusion Criteria:
	• Septic shock
	• Do-not-intubate orders
	
	Interventions:
	• Continuous infusion hydrocortisone 200 mg/day until Day 7, then hydrocortisone 100 mg/day for 4 days, and then hydrocortisone 50 mg/day for 3 days, for a total treatment duration of 14 days
	• Patients who showed clinical improvement by Day 4 were switched to a shorter 8-day regimen.
		Number of Participants:
		• ITT analysis (n = 149 participants): Hydrocortisone (n = 76) and placebo (n = 73)
		
		Participant Characteristics:
		• Mean age of participants was 62 years; 70% were men; median BMI was 28.
		• 96% of participants had confirmed SARS-CoV-2 infection.
		• Median symptom duration before randomization was 9 days in hydrocortisone group vs. 10 days in placebo group.
		• 81% of the patients overall were mechanically ventilated, and 24% in hydrocortisone group and 18% in placebo group were receiving vasopressors.
		• Among the patients receiving concomitant COVID-19 treatment, 3% received RDV, 14% LPV/RTV, 13% HCQ, and 34% HCQ plus AZM.
		• Median treatment duration was 10.5 days in hydrocortisone group vs. 12.8 days in placebo group (P = 0.25).
		
		Primary Outcome:
		• There was no difference in the proportion of patients with treatment failure by Day 21, which occurred in 32 of 76 patients (42.1%) in hydrocortisone group and 37 of 73 patients (50.7%) in placebo group (difference -8.6%; 95% CI, -24.9% to 7.7%; P = 0.29).
		
		Secondary Outcomes:
		• There was no difference between the groups in the need for intubation, rescue strategies, or oxygenation (i.e., change in PaO_2/FiO_2).
		  • Among the patients who did not require mechanical ventilation at baseline, 8 of 16 patients (50%) in hydrocortisone group required subsequent
			Limitations:
			• Small sample size. Planned sample size of 290, but 149 enrolled because study was terminated early after the release of results from the RECOVERY trial.
			• Limited information about comorbidities (e.g., hypertension)
			• Participants' race and/or ethnicity were not reported.
			• Nosocomial infections were recorded but not adjudicated.
			
			Interpretation:
			• Compared to placebo, hydrocortisone did not reduce treatment failure (defined as death or persistent respiratory support) at Day 21 in ICU patients with COVID-19 and acute respiratory failure.
			• Because this study was terminated early, it is difficult to make conclusions about the efficacy and safety of hydrocortisone therapy.
			• The starting dose of hydrocortisone used in this study were slightly higher than the 6 mg dose of dexamethasone used in the RECOVERY study. The hydrocortisone dose was adjusted according to clinical response.

Study Design	Methods	Results	Limitations and Interpretation
Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19: A Randomized Clinical Trial[5], continued			
	Primary Endpoint: • Treatment failure (defined as death or persistent dependency on mechanical ventilation or high-flow oxygen) by Day 21 **Secondary Endpoints:** • Need for intubation, rescue strategies, or oxygenation (i.e., change in PaO_2/FiO_2) • Nosocomial infections on Day 28 • Clinical status on Day 21	intubation vs. 12 of 16 (75%) in placebo group. • 3 SAEs were reported (cerebral vasculitis, cardiac arrest due to PE, and intra-abdominal hemorrhage from anticoagulation for PE); all occurred in the hydrocortisone group, but none were attributed to the intervention. • There was no difference between the groups in proportion of patients with nosocomial infections on Day 28. • In post hoc analysis, clinical status on Day 21 did not significantly differ between the groups except for fewer deaths in the hydrocortisone group (14.7% of patients died vs. 27.4% in placebo group; $P = 0.06$): • By Day 21, 57.3% of patients in hydrocortisone group vs. 43.8% in placebo group were discharged from the ICU and 22.7% in hydrocortisone group vs. 23.3% in placebo group were still mechanically ventilated.	
Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial (CAPE COD)[6]			
Randomized, embedded, multifactorial, adaptive platform trial of patients with severe COVID-19 (n = 403) Countries: Multinational	**Key Inclusion Criteria:** • Aged ≥18 years • Presumed or confirmed SARS-CoV-2 infection • ICU admission for respiratory or cardiovascular organ support **Key Exclusion Criteria:** • Presumed imminent death • Systemic corticosteroid use • >36 hours since ICU admission	**Number of Participants:** • mITT analysis (n = 384): Fixed-dose hydrocortisone (n=137), shock-based hydrocortisone (n = 146), and no hydrocortisone (n = 101) **Participant Characteristics:** • Mean age was 60 years. • 71% of patients were men. • Mean BMI was 29.7–30.9. • 50% to 64% of patients received mechanical ventilation.	**Limitations:** • Early termination following release of RECOVERY study results • Randomized study, but open label **Interpretation:** • Corticosteroids did not significantly increase support-free days in either the fixed-dose hydrocortisone or the shock-dependent hydrocortisone group, although the early termination of the trial led to limited power to detect difference between the study arms.

Study Design	Methods	Results	Limitations and Interpretation
Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial (CAPE COD)[6], continued			

	Interventions:
	• Hydrocortisone 50 mg 4 times daily for 7 days
	• Septic shock-based hydrocortisone 50 mg 4 times daily for the duration of shock
	• No hydrocortisone
	Primary Endpoint:
	• Days free of respiratory and cardiovascular organ support up to Day 21. (For this ordinal outcome, patients who died were assigned -1 day.)
	Secondary Endpoints:
	• In-hospital mortality
	• SAEs
		Primary Outcome:
		• No difference between the groups in organ-support free-days at Day 21 (median of 0 days in each group).
		• Compared to the no hydrocortisone group, median adjusted OR for the primary outcome:
		  • OR 1.43 (95% credible interval, 0.91–2.27) with 93% Bayesian probability of superiority for the fixed-dose hydrocortisone group
		  • OR 1.22 (95% credible interval, 0.76–1.94) with 80% Bayesian probability of superiority for the shock-based hydrocortisone group
		Secondary Outcomes:
		• No difference between the groups in mortality; 30%, 26%, and 33% of patients died in the fixed-dose, shock-based, and no hydrocortisone groups, respectively.
		• SAEs reported in 3%, 3%, and 1% of patients in the fixed-dose, shock-based, and no hydrocortisone groups, respectively.	

Efficacy Evaluation of Early, Low-Dose, Short-Term Corticosteroids in Adults Hospitalized with Non-Severe COVID-19 Pneumonia: A Retrospective Cohort Study[7]			
Retrospective cohort study in patients with nonsevere COVID-19 pneumonia and propensity score-matched controls (n = 55 matched case-control pairs) Country: China	**Key Inclusion Criteria:** • Confirmed COVID-19 • Pneumonia on chest CT scan • Aged ≥16 years **Key Exclusion Criteria:** • Severe pneumonia defined as having any of the following: respiratory distress, respiratory rates >30 breaths/min, SpO_2 <93%, oxygenation index <300 mm Hg, mechanical ventilation, or shock	**Number of Participants:** • Corticosteroids (n = 55): IV methylprednisolone (n=50) and prednisone (n = 5) • No corticosteroids (n = 55 matched controls chosen from 420 patients who did not receive corticosteroids) **Participant Characteristics:** • Median age was 58–59 years. • Median oxygen saturation was 95%. • 42% of patients in corticosteroids group and 46% in no corticosteroids group had comorbidities, including 35% to 36% with hypertension and 11% to 13% with diabetes.	**Limitations:** • Retrospective, case-control study • Small sample size (55 case-control pairs) • Corticosteroid therapy was selected preferentially for patients who had more risk factors for severe progression of COVID-19; the propensity score matching may not have adjusted for some of the unmeasured confounders.

Study Design	Methods	Results	Limitations and Interpretation
Efficacy Evaluation of Early, Low-Dose, Short-Term Corticosteroids in Adults Hospitalized with Non-Severe COVID-19 Pneumonia: A Retrospective Cohort Study[7], continued			

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

Key: AE = adverse event; ARDS = acute respiratory distress syndrome; AZM = azithromycin; BMI = body mass index; CT = computerized tomography; ECMO = extracorporeal membrane oxygenation; EU = European Union; HCQ = hydroxychloroquine; ICU = intensive care unit; IL = interleukin; ITT = intention-to-treat; IV = intravenous; LPV/RTV = lopinavir/ritonavir; mITT = modified intention-to-treat; the Panel = the COVID-19 Treatment Guidelines Panel; PaO_2/FiO_2 = ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; PE = pulmonary embolism; PEEP = positive end-expiratory pressure; PO = oral; RCT = randomized controlled trial; RDV = remdesivir; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOC = standard of care; SOFA = sequential organ failure assessment; SpO_2 = saturation of oxygen; WHO = World Health Organization

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

Last Updated: February 11, 2021

Janus Kinase Inhibitors

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

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

Recommendations

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

Rationale

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

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

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

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

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

Monitoring, Adverse Effects, and Drug-Drug Interactions

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

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

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

Considerations in Pregnancy

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

Considerations in Children

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

Baricitinib

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

Clinical Data for COVID-19

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

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

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

Clinical Trials

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

Ruxolitinib

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

Clinical Data for COVID-19

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

Clinical Trials

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

Tofacitinib

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

Clinical Data for COVID-19

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

Considerations in Pregnancy

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

Clinical Trials

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

Bruton's Tyrosine Kinase Inhibitors

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

Recommendation

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

Acalabrutinib

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

Clinical Data for COVID-19

Data regarding acalabrutinib are limited to the results from a retrospective case series of 19 patients with severe COVID-19.[21] Evaluation of the data to discern any clinical benefit is limited by the study's small sample size and lack of a control group.

Clinical Trials

Please check *ClinicalTrials.gov* 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[22] and to prevent chronic graft-versus-host disease in stem cell transplant recipients.[23] Based on results from a small case series, ibrutinib has been theorized to reduce inflammation and protect against ensuing lung injury in patients with COVID-19.[24]

Clinical Data for COVID-19

Data regarding ibrutinib are limited to those from an uncontrolled, retrospective case series of six patients with COVID-19 who were receiving the drug for a condition other than COVID-19.[24] Evaluation of the data for any clinical benefit is limited by the series' small sample size and lack of a control group.

Clinical Trials

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

Zanubrutinib

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

Clinical Data for COVID-19

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

Clinical Trials

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

Adverse Effects and Monitoring

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

Considerations in Pregnancy

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

Considerations in Children

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

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

Last Updated: February 11, 2021

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

Drug Name	Dosing Regimen *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
Corticosteroids					
Dexamethasone	**Dose for COVID-19:** • Dexamethasone 6 mg IV or PO once daily, for up to 10 days or until hospital discharge, whichever comes first[1]	• Hyperglycemia • Secondary infections • Reactivation of latent infections (e.g., HBV, HSV, strongyloidiasis, TB) • Psychiatric disturbances • Avascular necrosis • Adrenal insufficiency • Increased blood pressure	• Blood glucose • Blood pressure • Signs and symptoms of new infection • When initiating dexamethasone, consider appropriate screening and treatment to reduce the risk of *Strongyloides* hyperinfection in patients at high-risk of strongyloidiasis	• 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. • The approximate total daily dose equivalencies for these glucocorticoids to

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
Corticosteroids, continued					
Dexamethasone, continued		• Peripheral edema • Myopathy (particularly if used with neuromuscular blocking agents) • When used during outbreaks of other novel coronavirus infections (i.e., MERS and SARS), corticosteroid therapy was associated with delayed virus clearance.[2,3]	(e.g., patients from tropical, subtropical, or warm temperate regions or who engage in agricultural activities) or fulminant reactivations of HBV.[4-6]		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
Interferons					
Interferon Alfa	**PegIFN Alfa-2a Dose for MERS:** • PegIFN alfa-2a 180 mcg SQ once weekly for 2 weeks[7,8] **IFN Alfa-2b Dose for COVID-19 in Clinical Trials:** • Nebulized IFN alfa-2b 5 million international units twice daily (no duration listed in the study methods)[9]	• Flu-like symptoms (e.g., fever, fatigue, myalgia)[10] • Injection site reactions • Liver function abnormalities • Decreased blood counts • Worsening depression • Insomnia • Irritability • Nausea • Vomiting • Hypertension • Induction of autoimmunity	• 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. • Neither nebulized IFN alfa-2b nor IFN alfa-1b are FDA-approved for use in the United States. • Use with caution with other hepatotoxic agents.

Drug Name	Dosing Regimen *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 Alfa, continued					• Reduce dose if ALT >5 times ULN; discontin-ue if bilirubin level also increases. • Reduce dose or discontinue if neutropenia or thrombocytopenia occur. • A list of clinical trials is available: Interferon
Interferon Beta	**IFN Beta-1a Dose for MERS:** • IFN beta-1a 44 mcg SQ 3 times weekly[8] **Dose for COVID-19:** • Dose and duration unknown **IFN Beta-1b Dose for COVID-19:** • IFN beta-1b 8 million international units SQ every other day, up to 7 days total[11]	• Flu-like symptoms (e.g., fever, fatigue, myalgia)[12] • Leukopenia, neutropenia, thrombocytopenia, lymphopenia • Liver function abnormalities (ALT > AST) • Injection site reactions • Headache • Hypertonia • Pain • Rash • Worsening depression • Induction of autoimmunity	• 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 or 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 to moderate COVID-19. • **Use with caution** with other hepatotoxic agents. • Reduce dose if ALT >5 times ULN. • A list of clinical trials is available: Interferon **Availability:** • Several products are available in the United States; product doses differ.

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, continued					*IFN Beta-1a Products:* • Avonex, Rebif *IFN Beta-1b Products:* • Betaseron, Extavia
Interleukin-1 Inhibitor					
Anakinra	**Dose for Rheumatoid Arthritis:** • Anakinra 100 mg SQ once daily **Dose for COVID-19:** • Dose and duration vary by study • Has also been used as IV infusion	• Neutropenia (particularly with concomitant use of other agents that can cause neutropenia) • Anaphylaxis • Headache • Nausea • Diarrhea • Sinusitis • Arthralgia • Flu-like symptoms • Abdominal pain • Injection site reactions • Liver enzyme elevations	• 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[13]	**Dose for COVID-19 in Clinical Trial (See *ClinicalTrials.gov* Identifier NCT04315298):** • Sarilumab 400 mg IV (single dose)[14]	• Neutropenia, thrombocytopenia • Gastrointestinal perforation • HSR	• Monitor for HSR • Monitor for infusion reactions • Neutrophils • Platelets	• Elevated IL-6 may downregulate CYP enzymes; use of sarilumab may lead to increased metabolism of drugs that are	• For patients who are within 24 hours of admission to the ICU and who require invasive or noninvasive mechanical ventilation or high-flow oxygen (>0.4 FiO_2/30 L/min of oxygen

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-6 Inhibitors, continued					
Anti-Interleukin-6 Receptor Monoclonal Antibodies, continued					
Sarilumab[13]	• REMAP-CAP evaluated sarilumab for IV admin-istration, which is not the approved formula-tion in the United States.	• Increased liver enzymes • HBV reactivation • Infusion reaction possible	• Liver enzymes	CYP450 substrates. • Effects on CYP450 may persist for weeks after therapy.	flow), there are insufficient data to recommend either for or against the use of sarilumab for the treatment of COVID-19. • For patients who do not require ICU-level care or who are admitted to the ICU but do not meet the above criteria, the Panel **recommends against** the use of sarilumab for the treatment of COVID-19, except in a clinical trial **(BIIa)**. • Treatment with sarilumab may mask signs of acute inflammation or infection (i.e., by suppressing fever and CRP levels). • A list of clinical trials is available: Sarilumab
Tocilizumab[15]	**Dose for COVID-19 in Clinical Trial:** • Tocilizumab 8 mg/kg IV once • Dose **should not exceed** tocilizumab 800 mg. • If tocilizumab is used, administer with a course of dexamethasone therapy.	• Infusion-related reactions • HSR • Gastrointestinal perforation • Hepatotoxicity • Treatment-related changes in neutrophils, platelets, lipids, and liver enzymes	• 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.	• For patients who are within 24 hours of admission to the ICU and who require invasive or noninvasive mechanical ventilation or high-flow oxygen (>0.4 FiO_2/30 L/min of oxygen flow), there are insufficient data to recommend either for or against the use of tocilizumab for the treatment of COVID-19.

Drug Name	Dosing Regimen *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-6 Inhibitors, continued					
Anti-Interleukin-6 Receptor Monoclonal Antibodies, continued					
Tocilizumab[15], continued		• HBV reactivation			• Some Panel members would administer a single dose of tocilizumab (8 mg/kg actual body weight up to 800 mg) in addition to dexamethasone to patients who meet the above criteria and who are also exhibiting rapid progression of respiratory failure. • For patients who do not require ICU-level care or who are admitted to the ICU but do not meet the above criteria, the Panel **recommends against** the use of tocilizumab for the treatment of COVID-19, except in a clinical trial **(BIIa)**. • May mask signs of acute inflammation or infection (i.e., by suppressing fever and CRP levels). • The SQ formulation of tocilizumab **is not intended** for IV administration. • A list of clinical trials is available: Tocilizumab

Drug Name	Dosing Regimen *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-6 Inhibitors, continued					
Anti-Interleukin-6 Monoclonal Antibody					
Siltuximab	**Dose for Multicentric Castleman Disease:** • Siltuximab 11 mg/kg administered over 1 hour by IV infusion every 3 weeks[16] **Dose for COVID-19:** • Dose and duration unknown	• Infusion-related reaction • HSR • Gastrointestinal perforation • Neutropenia • Hypertension • Dizziness • Rash • Pruritus • Hyperuricemia	• Monitor for HSR • Monitor for infusion reactions • 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 **(AIIa)**. • May mask signs of acute inflammation or infection (i.e., by suppressing fever and CRP levels). • A list of clinical trials is available: Siltuximab
Kinase Inhibitors					
Bruton's Tyrosine Kinase Inhibitors					
Acalabrutinib	**Dose for FDA-Approved Indications:** • Acalabrutinib 100 mg PO every 12 hours **Dose for COVID-19:** • Dose and duration 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

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, continued					
Bruton's Tyrosine Kinase Inhibitors, continued					
Ibrutinib	**Dose for FDA-Approved Indications:** • Ibrutinib 420 mg or 560 mg PO once daily **Dose for COVID-19:** • Dose and duration 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** use in patients with severe baseline hepatic impairment. Dose modifications required in patients with mild or moderate hepatic impairment. • Patients with underlying cardiac risk factors, hypertension, or acute infections may be predisposed to cardiac arrhythmias. • A list of clinical trials is available: Ibrutinib
Zanubrutinib	**Dose for FDA-Approved Indications:** • Zanubrutinib 160 mg PO twice daily or 320 mg PO once daily **Dose for COVID-19:** • Dose and duration 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

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, continued					
Janus Kinase Inhibitors					

Baricitinib[17]	**Dose for Rheumatoid Arthritis:**
	• *Adults:* Baricitinib 2 mg PO once daily
	Dose for COVID-19:[18]
	• *Adults:* Baricitinib 4 mg PO once daily for 14 days or until hospital discharge
	• *Children:* Limited data are available. Dose per the FDA EUA:
	  • Aged ≥9 years: Baricitinib 4 mg PO once daily for 14 days or until hospital discharge
	  • Aged ≥2 years to <9 years: Baricitinib 2 mg PO once daily for 14 days or until hospital discharge
	• See full prescribing information for dosage recommendations in patients with renal impairment or hepatic impairment.[17]
		• Lymphoma and other malignancies
		• Thrombosis
		• Gastrointestinal perforation
		• Treatment-related changes in lymphocytes, neutrophils, Hgb, liver enzymes
		• HSV
		• 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.
				• **Avoid** administration of live vaccines.
					• There are insufficient data for the Panel to recommend either for or against the use of baricitinib in combination with RDV for the treatment of COVID-19 in hospitalized patients, when corticosteroids can be used.
					• In the rare circumstance when corticosteroids cannot be used, the Panel recommends baricitinib in combination with RDV for the treatment of COVID-19 in hospitalized nonintubated patients who require oxygen supplementation **(BIIa)**.
					• The Panel **recommends against** the use of baricitinib without RDV, except in a clinical trial **(AIII)**.
					• There are insufficient data for the Panel to recommend either for or against the use of baricitinib in combination with corticosteroids for the treatment of COVID-19. Because both agents are potent immunosuppressants, there is a potential for an additive risk of infection.
					• Baricitinib **is not recommended** for patients with severe hepatic or renal impairment.

Drug Name	Dosing Regimen *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, continued					
Janus Kinase Inhibitors, continued					
Baricitinib[17], continued					• Baricitinib is available through the FDA EUA for the treatment of COVID-19 in combination with RDV for hospitalized adults and pediatric patients aged ≥2 years who require supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation.[18] • A list of clinical trials is available: Baricitinib
Ruxolitinib	**Dose for FDA-Approved Indications:** • Ruxolitinib 5 mg– 20 mg PO twice daily **Dose for COVID-19 in Clinical Trials:** • Ruxolitinib 5 mg– 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 doses of fluconazole >200 mg.	• The Panel **recommends against** the use of JAK inhibitors (other than baricitinib) for the treatment of COVID-19, except in a clinical trial **(AIII)**. • Dose modification may be required in patients with moderate or severe renal impairment, hepatic impairment, or thrombocytopenia. • A list of clinical trials is available: Ruxolitinib

Drug Name	Dosing Regimen *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, continued					
Janus Kinase Inhibitors, continued					
Tofacitinib	**Dose for FDA-Approved Indications:** • Tofacitinib 5 mg PO twice daily for rheumatoid and psoriatic arthritis • Tofacitinib 10 mg PO twice daily for ulcerative colitis **Dose for COVID-19:** • Dose and duration unknown; a planned COVID-19 clinical trial will evaluate 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 • 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 (other than baricitinib) 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
Non-SARS-CoV-2 Specific Immunoglobulin					
Non-SARS-CoV-2 Specific Immunoglobulin	• Dose varies 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 • Monitor 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. • A list of clinical trials is available: Intravenous 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
Non-SARS-CoV-2 Specific Immunoglobulin, continued					
Non-SARS-CoV-2 Specific Immunoglobulin, continued		• AEs may vary by formulation. • AEs may be increased with high-dose, rapid infusion, or in patients with underlying conditions.			

Key: AE = adverse effect or adverse event; ALC = absolute lymphocyte count; ALT = alanine transaminase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BTK = Bruton's tyrosine kinase; CBC = complete blood count; CHF = congestive heart failure; CrCl = creatinine clearance; CPK = creatine phosphokinase; CRP = C-reactive protein; CYP = cytochrome P; DVT = deep vein thrombosis; EIND = Emergency Investigational New Drug; EUA = Emergency Use Authorization; FDA = Food and Drug; FiO_2 = fraction of inspired oxygen; 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; PEG-IFN = pegylated interferon; PK = pharmacokinetic; PO = orally; PPI = proton pump inhibitor; REMAP-CAP = A Randomised, Embedded, Multi-Factorial, Adaptive Platform Trial for Community-Acquired Pneumonia; RDV = remdesivir; SARS = severe acute respiratory syndrome; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SQ = subcutaneous; TACO = transfusion-associated circulatory overload; TB = tuberculosis; the Panel = the COVID-19 Treatment Guidelines Panel; TNF = tumor necrosis factor; TRALI = transfusion-related acute lung injury; ULN = upper limit of normal

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Antithrombotic Therapy in Patients with COVID-19

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Summary Recommendations
Laboratory Testing • In nonhospitalized patients with COVID-19, there are currently no data to support the measurement of coagulation markers (e.g., D-dimers, prothrombin time, platelet count, fibrinogen) **(AIII)**. • In hospitalized patients with COVID-19, hematologic and coagulation parameters are commonly measured, although there are currently insufficient data to recommend either for or against using this data to guide management decisions. **Chronic Anticoagulant and Antiplatelet Therapy** • Patients who are receiving anticoagulant or antiplatelet therapies for underlying conditions should continue these medications if they receive a diagnosis of COVID-19 **(AIII)**. **Venous Thromboembolism Prophylaxis and Screening** • For nonhospitalized patients with COVID-19, anticoagulants and antiplatelet therapy should not be initiated for the prevention of venous thromboembolism (VTE) or arterial thrombosis unless the patient has other indications for the therapy or is participating in a clinical trial **(AIII)**. • Hospitalized nonpregnant adults with COVID-19 should receive prophylactic dose anticoagulation **(AIII)** (see the recommendations for pregnant individuals below). Anticoagulant or antiplatelet therapy should not be used to prevent arterial thrombosis outside of the usual standard of care for patients without COVID-19 **(AIII)**. • There are currently insufficient data to recommend either for or against the use of thrombolytics or higher than the prophylactic dose of anticoagulation for VTE prophylaxis in hospitalized COVID-19 patients outside of a clinical trial. • Hospitalized patients with COVID-19 should not routinely be discharged from the hospital while on VTE prophylaxis **(AIII)**. Continuing anticoagulation with a Food and Drug Administration-approved regimen for extended VTE prophylaxis after hospital discharge can be considered for patients who are at low risk for bleeding and high risk for VTE, as per the protocols for patients without COVID-19 (see details on defining at-risk patients below) **(BI)**. • There are currently insufficient data to recommend either for or against routine deep vein thrombosis screening in COVID-19 patients without signs or symptoms of VTE, regardless of the status of their coagulation markers. • For hospitalized COVID-19 patients who experience rapid deterioration of pulmonary, cardiac, or neurological function, or of sudden, localized loss of peripheral perfusion, the possibility of thromboembolic disease should be evaluated **(AIII**). **Hospitalized Children With COVID-19** • For hospitalized children with COVID-19, indications for VTE prophylaxis should be the same as those for children without COVID-19 **(BIII)**. **Treatment** • When diagnostic imaging is not possible, patients with COVID-19 who experience an incident thromboembolic event or who are highly suspected to have thromboembolic disease should be managed with therapeutic doses of anticoagulant therapy **(AIII)**. • Patients with COVID-19 who require extracorporeal membrane oxygenation or continuous renal replacement therapy or who have thrombosis of catheters or extracorporeal filters should be treated with antithrombotic therapy as per the standard institutional protocols for those without COVID-19 **(AIII)**. **Special Considerations During Pregnancy and Lactation** • If antithrombotic therapy is prescribed during pregnancy prior to a diagnosis of COVID-19, this therapy should be continued **(AIII)**. • For pregnant patients hospitalized for severe COVID-19, prophylactic dose anticoagulation is recommended unless contraindicated (see below) **(BIII)**.

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

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

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

Association Between COVID-19 and Thromboembolism

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

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

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

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

hospitalized COVID-19 patients from a single center in the United States reported in-hospital mortality in 22.5% of patients who received therapeutic anticoagulation and 22.8% of patients who did not receive anticoagulation. The study further reported that in a subset of 395 mechanically ventilated patients, 29.1% of the patients who received anticoagulation and 62.7% of those who did not receive anticoagulation died. The study had important limitations: it lacked details on patient characteristics, indications for anticoagulant initiation, and descriptions of other therapies that the patients received that may have influenced mortality. In addition, the authors did not discuss the potential impact of survival bias on the study results. For these reasons, the data are not sufficient to influence standard of care, and this study further emphasizes the need for prospective trials to define the risks and potential benefits of therapeutic anticoagulation in patients with COVID-19.[18] Three international trials (Antithrombotic Therapy to Ameliorate Complications of COVID-19 [ATTACC], Therapeutic Anticoagulation; Accelerating COVID-19 Therapeutic Interventions and Vaccines-4 [ACTIV-4], and the Randomized, Embedded, Multi-factorial Adaptive Platform Trial for Community-Acquired Pneumonia [REMAP-CAP]) compared the effectiveness of therapeutic dose anticoagulation and prophylactic dose anticoagulation in reducing the need for organ support over 21 days in moderately ill or critically ill adults hospitalized for COVID-19. The need for organ support was defined as requiring high-flow nasal oxygen, invasive or noninvasive mechanical ventilation, vasopressor therapy, or extracorporeal membrane oxygenation (ECMO). The trials paused enrollment of patients requiring intensive care unit (ICU)-level care after an interim pooled analysis demonstrated futility of therapeutic anticoagulation in improving organ support, and a concern for safety. The results of the interim analysis are available on the ATTACC website. Unblinded data and additional study outcomes, including the occurrence of thrombosis, are expected to be reported soon.[19]

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

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

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

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

Monitoring Coagulation Markers in Patients With COVID-19

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

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

Managing Antithrombotic Therapy in Patients With COVID-19

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

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

Chronic Anticoagulant or Antiplatelet Therapy

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

Patients with COVID-19 Who Are Managed as Outpatients

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

Hospitalized Patients With COVID-19

For hospitalized patients with COVID-19, prophylactic dose anticoagulation should be prescribed unless contraindicated (e.g., a patient has active hemorrhage or severe thrombocytopenia) **(AIII)**. Although data supporting this recommendation are limited, a retrospective study showed reduced mortality in patients who received prophylactic anticoagulation, particularly if the patient had a sepsis-induced coagulopathy score ≥4.[4] For those without COVID-19, anticoagulant or antiplatelet therapy should not be used to prevent arterial thrombosis outside of the standard of care **(AIII)**. Anticoagulation is routinely used to prevent arterial thromboembolism in patients with heart arrhythmias. Although there are reports of strokes and myocardial infarction in patients with COVID-19, the incidence of these events is unknown.

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

There are currently insufficient data to recommend either for or against the use of thrombolytic agents or higher than the prophylactic dose of anticoagulation for VTE prophylaxis for hospitalized patients with COVID-19 outside of a clinical trial. Three international trials (ACTIV-4, REMAP-CAP, and ATTACC) compared the effectiveness of therapeutic dose anticoagulation and prophylactic dose anticoagulation in reducing the need for organ support over 21 days in moderately ill or critically ill adults hospitalized for COVID-19. The need for organ support was defined as requiring high-flow nasal oxygen, invasive or noninvasive mechanical ventilation, vasopressor therapy, or ECMO. The trials paused enrollment of patients requiring ICU-level care at enrollment after an interim pooled analysis demonstrated futility of therapeutic anticoagulation in reducing the need for organ support and a concern for safety. The results of the interim analysis are available on the ATTACC website. Unblinded data and additional study outcomes, including the occurrence of thrombosis, are expected to be reported soon.[19]

Although there is evidence that multi-organ failure is more likely in patients with sepsis who develop coagulopathy,[30] there is no convincing evidence to show that any specific antithrombotic treatment will influence outcomes in those with or without COVID-19. Participation in randomized trials is encouraged.

Patients with COVID-19 who require ECMO or continuous renal replacement therapy or who have thrombosis of catheters or extracorporeal filters should be treated as per the standard institutional protocols for those without COVID-19 **(AIII)**.

Hospitalized Children With COVID-19

A recent meta-analysis of publications on COVID-19 in children did not discuss VTE.[31] Indications for VTE prophylaxis in hospitalized children with COVID-19 should be the same as those for hospitalized children without COVID-19 **(BIII)**.

Patients With COVID-19 Who Are Discharged from the Hospital

VTE prophylaxis after hospital discharge **is not recommended** for patients with COVID-19 **(AIII)**. For certain high-VTE risk patients without COVID-19, post-discharge prophylaxis has been shown to be beneficial. The Food and Drug Administration approved the use of rivaroxaban 10 mg daily for 31 to 39 days in these patients.[32,33] Inclusion criteria for the trials that studied post-discharge VTE prophylaxis included:

- Modified International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) VTE risk score ≥4; *or*
- Modified IMPROVE VTE risk score ≥2 and D-dimer level >2 times the upper limit of normal.[32]

Any decision to use post-discharge VTE prophylaxis for patients with COVID-19 should include consideration of the individual patient's risk factors for VTE, including reduced mobility, bleeding risks, and feasibility. Participation in clinical trials is encouraged.

Special Considerations During Pregnancy and Lactation

Because pregnancy is a hypercoagulable state, the risk of thromboembolism is greater in pregnant individuals than in nonpregnant individuals.[34] It is not yet known whether COVID-19 increases this risk. In several cohort studies of pregnant women with COVID-19 in the United States and Europe,

VTE was not reported as a complication even among women with severe disease, although the receipt of prophylactic or therapeutic anticoagulation varied across the studies.[35-37] The American College of Obstetricians and Gynecologists (ACOG) advises that, although there are no data for or against thromboprophylaxis in the setting of COVID-19 in pregnancy, VTE prophylaxis can reasonably be considered for pregnant women hospitalized with COVID-19, particularly for those who have severe disease.[38] If there are no contraindications to use, the Society of Maternal Fetal Medicine recommends prophylactic heparin or low molecular weight heparin in critically ill or mechanically ventilated pregnant patients.[39] Several professional societies, including the American Society of Hematology and ACOG, have guidelines that specifically address the management of VTE in the context of pregnancy.[40,41] If delivery is threatened, or if there are other risks for bleeding, the risk of bleeding may outweigh the potential benefit of VTE prophylaxis in pregnancy.

There are no data on the use of scoring systems to predict VTE risk in pregnant individuals. Additionally, during pregnancy, the D-dimer level may not be a reliable predictor of VTE because there is a physiologic increase of D-dimer levels throughout gestation.[42-44]

In general, the preferred anticoagulants during pregnancy are heparin compounds. Because of its reliability and ease of administration, low-molecular weight heparin is recommended, rather than unfractionated heparin, for the prevention and treatment of VTE in pregnancy.[41]

Direct-acting anticoagulants are not routinely used during pregnancy due to the lack of safety data in pregnant individuals.[40] The use of warfarin to prevent or treat VTE should be avoided in pregnant individuals, regardless of their COVID-19 status, and especially during the first trimester due to the concern for teratogenicity.

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

- If antithrombotic therapy is prescribed during pregnancy prior to a diagnosis of COVID-19, this therapy should be continued **(AIII)**.
- For pregnant patients hospitalized for severe COVID-19, prophylactic dose anticoagulation is recommended unless contraindicated **(BIII)**.
- Like for nonpregnant patients, VTE prophylaxis after hospital discharge **is not recommended** for pregnant patients **(AIII)**. Decisions to continue VTE prophylaxis in the pregnant or postpartum patient should be individualized, considering concomitant VTE risk factors.
- Anticoagulation therapy use during labor and delivery requires specialized care and planning. It should be managed in pregnant patients with COVID-19 in a similar way as in pregnant patients with other conditions that require anticoagulation in pregnancy **(AIII)**.
- Unfractionated heparin, low molecular weight heparin, and warfarin do not accumulate in breast milk and do not induce an anticoagulant effect in the newborn; therefore, they can be used by breastfeeding women with or without COVID-19 who require VTE prophylaxis or treatment **(AIII)**. In contrast, use of direct-acting oral anticoagulants during pregnancy is not routinely recommended due to lack of safety data **(AIII)**.[40]

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Supplements

Last Updated: February 11, 2021

Summary Recommendations
Vitamin C • 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. **Vitamin D** • There are insufficient data for the Panel to recommend either for or against the use of vitamin D for the treatment of COVID-19. **Zinc** • There are insufficient data for the Panel to recommend either for or against the use of zinc for the treatment of COVID-19. • The Panel **recommends against** using zinc supplementation above the recommended dietary allowance for the prevention of COVID-19, except in a clinical trial **(BIII)**.
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 ob-servational cohort studies; III = Expert opinion

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

Some clinicians advocate for the use of vitamin and mineral supplements to treat respiratory viral infections. Ongoing studies are evaluating the use of vitamin and mineral supplements for both the treatment and prevention of severe acute respiratory syndrome coronavirus 2 infection.

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

Vitamin C

Last Updated: November 3, 2020

Vitamin C (ascorbic acid) is a water-soluble vitamin that is thought to have beneficial effects in patients with severe and critical illnesses. It is an antioxidant and free radical scavenger that has anti-inflammatory properties, influences cellular immunity and vascular integrity, and serves as a cofactor in the generation of endogenous catecholamines.[1,2] Because humans may require more vitamin C in states of oxidative stress, vitamin C supplementation has been evaluated in numerous disease states, including serious infections and sepsis. Because serious COVID-19 may cause sepsis and acute respiratory distress syndrome (ARDS), the potential role of high doses of vitamin C in ameliorating inflammation and vascular injury in patients with COVID-19 is being studied.

Recommendation for Non-Critically Ill Patients With COVID-19

- There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of vitamin C for the treatment of COVID-19 in non-critically ill patients.

Rationale

Because patients who are not critically ill with COVID-19 are less likely to experience oxidative stress or severe inflammation, the role of vitamin C in this setting is unknown.

Recommendation for Critically Ill Patients With COVID-19

- There are insufficient data for the Panel to recommend either for or against the use of vitamin C for the treatment of COVID-19 in critically ill patients.

Rationale

There are no completed controlled trials of vitamin C in patients with COVID-19, and the available observational data are sparse and inconclusive. Studies of vitamin C in sepsis patients and ARDS patients have reported variable efficacy and few safety concerns.

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

Intravenous Vitamin C Alone

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

In a randomized controlled trial in critically ill patients with sepsis-induced ARDS (n = 167), patients who received IV vitamin C 200 mg/kg per day for 4 days had SOFA scores and levels of inflammatory markers that were similar to those observed in patients who received placebo. However, 28-day mortality was lower in the treatment group (29.8% vs. 46.3%; $P = 0.03$), coinciding with more days alive and free of the hospital and the intensive care unit.[4] A post hoc analysis of the study data reported a difference in median SOFA scores between the treatment group and placebo group at 96 hours; however, this difference was not present at baseline or 48 hours.[5]

Intravenous Vitamin C Plus Thiamine With or Without Hydrocortisone

Two small studies that used historic controls reported favorable clinical outcomes (i.e., reduced mortality, reduced risk of progression to organ failure, and improved radiographic findings) in patients with sepsis or severe pneumonia who received a combination of vitamin C, thiamine, and hydrocortisone.[6,7]

Three recent randomized trials in which patients received vitamin C and thiamine (with or without hydrocortisone) to treat sepsis and septic shock showed that this combination conferred benefits for certain clinical parameters. However, no survival benefit was reported. Two trials observed reductions in organ dysfunction (as measured by a SOFA score at Day 3)[8,9] or the duration of 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: February 11, 2021

Recommendations

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

Rationale

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

Several clinical trials are currently investigating the use of zinc supplementation alone or in combination with hydroxychloroquine for the prevention and treatment of COVID-19 (see *ClinicalTrials.gov* for more information about ongoing studies). The recommended dietary allowance for elemental zinc is 11 mg daily for men and 8 mg for nonpregnant women.[5] The doses used in registered clinical trials for patients with COVID-19 vary between studies, with a maximum dose of zinc sulfate 220 mg (50 mg of elemental zinc) twice daily. However, there are currently insufficient data to recommend either for or against the use of zinc for the treatment of COVID-19.

Long-term zinc supplementation can cause copper deficiency with subsequent reversible hematologic defects (i.e., anemia, leukopenia) and potentially irreversible neurologic manifestations (i.e., myelopathy, paresthesia, ataxia, spasticity).[6,7] The use of zinc supplementation for durations as short as 10 months has been associated with copper deficiency.[4] In addition, oral zinc can decrease the absorption of medications that bind with polyvalent cations.[5] Because zinc has not been shown to have a clinical benefit and may be harmful, the Panel **recommends against** using **zinc** supplementation above the recommended dietary allowance for the prevention of COVID-19, except in a clinical trial **(BIII)**.

Clinical Data

Randomized Clinical Trial of Zinc Plus Hydroxychloroquine Versus Hydroxychloroquine Alone in Hospitalized Patients With COVID-19

In a randomized clinical trial conducted at three academic medical centers in Egypt, 191 patients with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection were randomized to receive either zinc 220 mg twice daily plus hydroxychloroquine or hydroxychloroquine alone for a 5-day course. The primary endpoints were recovery within 28 days, the need for mechanical ventilation, and death. The two groups were matched for age and gender.[8]

Results

- There were no significant differences between the two arms in the percentages of patients who recovered within 28 days (79.2% in the hydroxychloroquine plus zinc arm vs. 77.9% in the

hydroxychloroquine only arm; $P = 0.969$), the need for mechanical ventilation ($P = 0.537$), or overall mortality ($P = 0.986$).

- The only risk factors for mortality were age and the need for mechanical ventilation.

Limitations

- This study had a relatively small sample size.

Interpretation

A moderately sized randomized clinical trial failed to find a clinical benefit for the combination of zinc and hydroxychloroquine.

Observational Study of Zinc Supplementation in Hospitalized Patients

A retrospective study enrolled 242 patients with polymerase chain reaction-confirmed SARS-CoV-2 infection who were admitted to Hoboken University Medical Center. One hundred and ninety-six patients (81.0%) received a total daily dose of zinc sulfate 440 mg (100 mg of elemental zinc); of those, 191 patients (97%) also received hydroxychloroquine. Among the 46 patients who did not receive zinc, 32 patients (70%) received hydroxychloroquine. The primary outcome was days from hospital admission to in-hospital mortality, and the primary analysis explored the causal association between zinc therapy and survival.[9]

Results

- There were no significant differences in baseline characteristics between the groups. In the zinc group, 73 patients (37.2%) died compared with 21 patients (45.7%) in the control group. In the primary analysis, which used inverse probability weighting (IPW), the effect estimate of zinc therapy was an additional 0.84 days of survival (95% CI, -1.51 days to 3.20 days; $P = 0.48$).
- In a multivariate Cox regression analysis with IPW, the use of zinc sulfate was not significantly associated with a change in the risk of in-hospital mortality (aHR 0.66; 95% CI, 0.41–1.07; $P = 0.09$).
- Older age, male sex, and severe or critical COVID-19 were significantly associated with an increased risk of in-hospital mortality.

Limitations

- This is a retrospective study; patients were not randomized to receive zinc supplementation or to receive no zinc.

Interpretation

This single-center, retrospective study failed to find a mortality benefit in patients who received zinc supplementation.

Multicenter Retrospective Cohort Study That Compared Hospitalized Patients Who Received Zinc Plus Hydroxychloroquine to Those Who Did Not

This study has not been peer reviewed.

This multicenter retrospective cohort study of hospitalized adults with SARS-CoV-2 infection who were admitted to four New York City hospitals between March 10 and May 20, 2020, compared patients who received zinc plus hydroxychloroquine to those who received treatment that did not include this combination.[10]

Results

- The records of 3,473 patients were reviewed.
- The median patient age was 64 years; 1,947 patients (56%) were male, and 522 patients (15%) were mechanically ventilated.
- Patients who received an interleukin-6 inhibitor or remdesivir were excluded from the analysis.
- A total of 1,006 patients (29%) received zinc plus hydroxychloroquine, and 2,467 patients (71%) received hydroxychloroquine without zinc.
- During the study, 545 patients (16%) died. In univariate analyses, mortality rates were significantly lower among patients who received zinc plus hydroxychloroquine than among those who did not (12% vs. 17%; $P < 0.001$). Similarly, hospital discharge rates were significantly higher among patients who received zinc plus hydroxychloroquine than among those who did not (72% vs. 67%; $P < 0.001$).
- In a Cox regression analysis that adjusted for confounders, treatment with zinc plus hydroxychloroquine was associated with a significantly reduced risk of in-hospital death (aHR 0.76; 95% CI, 0.60–0.96; $P = 0.023$). Treatment with zinc alone (n = 1,097) did not affect mortality (aHR 1.14; 95% CI, 0.89–1.44; $P = 0.296$), and treatment with hydroxychloroquine alone (n = 2,299) appeared to be harmful (aHR 1.60; 95% CI, 1.22–2.11; $P = 0.001$).
- There were no significant interactions between zinc plus hydroxychloroquine and other COVID-19-specific medications.

Limitations

- This is a retrospective review; patients were not randomized to receive zinc plus hydroxychloroquine or to receive other treatments.
- The authors do not have data on whether patients were taking zinc and/or hydroxychloroquine prior to study admission.
- The groups were not balanced; recipients of zinc plus hydroxychloroquine were more likely to be male, Black, or to have a higher body mass index and diabetes. Patients who received zinc plus hydroxychloroquine were also treated with corticosteroids and azithromycin more often and treated with lopinavir/ritonavir less often than those who did not receive this drug combination.

Interpretation

In this preprint, the use of zinc plus hydroxychloroquine was associated with decreased rates of in-hospital mortality, but neither zinc alone nor hydroxychloroquine alone reduced mortality. Treatment with hydroxychloroquine alone appeared to be harmful.

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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)**.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional **Rating of Evidence:** I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

Recommendations

- Persons with COVID-19 who are prescribed angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) for cardiovascular disease (or other indications) should continue these medications **(AIII)**.
- The COVID-19 Treatment Guidelines Panel (the Panel) recommends against the use of ACE inhibitors or ARBs for the treatment of COVID-19, except in a clinical trial **(AIII)**.

Angiotensin-converting enzyme 2 (ACE2) is the cell surface receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It has been 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 the pregnancy considerations subsection of each individual section of the Guidelines.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional **Rating of Evidence:** I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

Epidemiology of COVID-19 in Pregnancy

Initial reports of COVID-19 disease acquired in the third trimester were reassuring, although most early data were limited to case reports and case series.[5-7] Since that time, a large population-based cohort study in the United Kingdom evaluated outcomes in pregnant women hospitalized with confirmed severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infection. Among 427 pregnant women admitted to 197 obstetric units across the United Kingdom, the rates of critical care admission and severe SARS-CoV-2-associated maternal mortality were similar to those in the general population of women of reproductive age hospitalized with COVID-19 in the United Kingdom, although the pregnant women were not compared with age-matched, nonpregnant controls.[8]

In June 2020, the Centers for Disease Control and Prevention (CDC) released surveillance data evaluating SARS-CoV-2-related outcomes in reproductive aged women by pregnancy status. Among 326,335 women aged 15 to 44 years with positive test results for SARS-CoV-2, pregnant women were more likely to be hospitalized, be admitted to an intensive care unit (ICU), and receive mechanical ventilation. However, the overall absolute increase in rates of ICU admission and mechanical ventilation was low among the pregnant women and the nonpregnant women (1.5% vs. 0.9% for ICU admission, respectively, and 0.5% vs 0.3% for mechanical ventilation, respectively). COVID-19-related death rates were similar in the pregnant and nonpregnant populations. Pregnancy outcomes such as preterm birth or pregnancy loss were not evaluated.

This analysis has a number of significant limitations, including:

- Pregnancy status was only available for 28% of the women of reproductive age with SARS-CoV-2 infection.
- It was not possible to determine whether the reasons for hospitalization, ICU admission, or mechanical ventilation were related to COVID-19, pregnancy, and/or delivery.

Pregnant women who are Hispanic or Black may be disproportionately affected by SARS-CoV-2 infection.[9] Pregnant women should be counseled about the potential for severe disease from SARS-CoV-2 and measures to protect themselves and their families from infection, including physical distancing, face coverings, and hand hygiene. CDC, ACOG, and SMFM highlight the importance of accessing prenatal care. ACOG provides an FAQ on using telehealth to deliver antenatal care, when appropriate.

ACOG has developed an algorithm to evaluate and manage pregnant outpatients with suspected or confirmed SARS-CoV-2 infection. As in nonpregnant patients, SARS-CoV-2 infection in pregnant patients can present as asymptomatic/presymptomatic disease or with a wide range of clinical manifestations, from mild symptoms that can be managed with supportive care at home to severe disease and respiratory failure requiring ICU admission. As with other patients, in the pregnant patient with symptoms compatible with COVID-19, the illness severity, underlying comorbidities, and clinical status should all be assessed to determine whether in-person evaluation for potential hospitalization is needed.

If hospitalization is indicated, care should be provided in a facility that can conduct maternal and fetal monitoring, when appropriate. The management of COVID-19 in the pregnant patient may include:

- Fetal and uterine contraction monitoring, when appropriate, based on gestational age
- Individualized delivery planning
- A multispecialty, team-based approach that may include consultation with obstetric, maternal-fetal medicine, infectious disease, pulmonary and critical care, and pediatric specialists, as appropriate.

Other recommendations on the management of COVID-19, as outlined for the nonpregnant patient, also apply in pregnancy.

Timing of Delivery

- Detailed guidance relating to timing of delivery and risk of vertical transmission of SARS-CoV-2 is provided by ACOG.[10]
- In most cases, the timing of delivery should be dictated by obstetric indications rather than maternal diagnosis of COVID-19. For women who had suspected or confirmed COVID-19 early in pregnancy who recover, no alteration to the usual timing of delivery is indicated.
- Vertical transmission of SARS-CoV-2 via the transplacental route appears to be rare but possible.[11-13]

Management of COVID-19 in the Setting of Pregnancy

- Potentially effective treatment for COVID-19 should not be withheld from pregnant women because of theoretical concerns related to the safety of therapeutic agents in pregnancy **(AIII)**.
- Decisions regarding the use of drugs approved for other indications or investigational agents for the treatment of COVID-19 in pregnant patients must be made with shared decision-making between the patient and the clinical team, considering the safety of the medication for the woman

and the fetus and the severity of maternal disease. For detailed guidance on the use of COVID-19 therapeutic agents in pregnancy, please refer to the pregnancy considerations subsection of each individual section of the Guidelines.

- To date, most SARS-CoV-2-related clinical trials have excluded, or included only a very few, pregnant women and lactating women. This limitation makes it difficult to make evidence-based recommendations on the use of SARS-CoV-2 therapies in these vulnerable patients and potentially limits their COVID-19 treatment options. When possible, pregnant women and lactating women should not be excluded from clinical trials of therapeutic agents or vaccines for SARS-CoV-2 infection.

Post-Delivery

- Specific guidance for post-delivery management of infants born to mothers with known or suspected SARS-CoV-2 infection, including breastfeeding recommendations, is provided by the CDC[14,15] and the American Academy of Pediatrics.[16]

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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 considerations in children subsection of each individual section of the Guidelines for more information on using these drugs in children.

Multisystem Inflammatory Syndrome in Children

Emerging reports from Europe and the United States have suggested that COVID-19 may be associated with MIS-C (also referred to as pediatric multisystem inflammatory syndrome–temporally associated with SARS-CoV-2 [PMIS-TS]). The syndrome was first described in the United Kingdom, where previously healthy children with severe inflammation and Kawasaki disease-like features were identified

to have current or recent infection with SARS-CoV-2.[16,17] Additional cases of MIS-C have been reported in other European countries, including Italy and France.[18,19] Emerging data suggest that MIS-C may be associated with pediatric patients who are slightly older than children typically seen with Kawasaki disease, and some cases of MIS-C in young adults have been reported.

In the United States, from April 16 through May 4, 2020, the New York City Department of Health and Mental Hygiene received reports of 15 hospitalized children with clinical presentation consistent with MIS-C. Subsequently, the New York State Department of Health has been investigating several hundred cases and a few deaths in children with similar presentations, many of whom tested positive for SARS-CoV-2 infection by reverse transcriptase polymerase chain reaction (PCR) or serology.[20] Several other states are now reporting cases consistent with MIS-C.

The current case definition for MIS-C can be found on the CDC website. This case definition, which may evolve as more data become available, includes:

- Fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multiorgan involvement, *and*
- No alternate diagnosis, *and*
- Recent or current SARS-CoV-2 infection or exposure to COVID-19.

From the available data, patients with MIS-C present with persistent fever, evidence of systemic inflammation, and a variety of signs and symptoms of multiorgan system involvement, including cardiac, gastrointestinal, renal, hematologic, dermatologic, and neurologic involvement.

Some patients who meet criteria for MIS-C also meet criteria for complete or incomplete Kawasaki disease. An observational study compared data from Italian children with Kawasaki-like illness that was diagnosed before and after the onset of the SARS-CoV-2 epidemic. The data suggest that the SARS-CoV-2-associated cases occurred in children who were older than the children with Kawasaki-like illness diagnosed prior to the COVID-19 epidemic. In addition, the rates of cardiac involvement, associated shock, macrophage activation syndrome, and need for adjunctive steroid treatment were higher for the SARS-CoV-2-associated cases.[18] Many patients with MIS-C have abnormal markers of cardiac injury or dysfunction, including troponin and brain natriuretic protein. Echocardiographic findings include impaired left ventricular function, as well as coronary artery dilations, and rarely, coronary artery aneurysms. At presentation, few patients are SARS-CoV-2 PCR positive (nasopharyngeal or nasal swab or stool sample), but most have detectable antibodies to SARS-CoV-2. Emerging observations suggest that there may be a wider range of severity of symptoms than initially recognized. Epidemiologic and clinical data suggest that MIS-C may represent a post-infectious inflammatory phenomenon rather than a direct viral process. The role of asymptomatic infection and the pattern of timing between SARS-CoV-2 infection and MIS-C are not well understood, and currently a causal relationship is not established.

Currently, there is limited information available about risk factors, pathogenesis, clinical course, and treatment for MIS-C. Supportive care remains the mainstay of therapy. There are currently insufficient data for the COVID-19 Treatment Guidelines Panel to recommend either for or against any therapeutic strategy for the management of MIS-C. Although no definitive data are available, many centers consider the use of intravenous immune globulin, steroids, and other immunomodulators (including interleukin-1 and interleukin-6 inhibitors) for therapy, and antiplatelet and anticoagulant therapy. The role of antiviral medications that specifically target SARS-CoV-2 is not clear at this time. MIS-C management decisions should involve a multidisciplinary team of pediatric specialists in intensive care, infectious diseases, cardiology, hematology, and rheumatology.

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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 Immunomodulators Under Evaluation for the Treatment of COVID-19). • Clinicians should pay careful attention to potential drug-drug interactions and overlapping toxicities between drugs that are used to treat COVID-19 and cancer-directed therapies, prophylactic antimicrobials, corticosteroids, and other medications **(AIII)**. • Clinicians who are treating COVID-19 in patients with cancer should consult with a hematologist or oncologist before adjusting cancer-directed medications **(AIII)**. • Decisions about administering cancer-directed therapy during SARS-CoV-2 infection should be made on a case-by-case basis; clinicians should consider the indication for chemotherapy, the goals of care, and the patient's history of tolerance to the treatment **(BIII)**.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional **Rating of Evidence:** I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

People who are being treated for cancer may be at increased risk of severe COVID-19, and their outcomes are worse than individuals without cancer.[1-4] A meta-analysis of 46,499 patients with COVID-19 showed that all-cause mortality (risk ratio 1.66; 95% CI, 1.33–2.07) was higher in patients with cancer, and that patients with cancer were more likely to be admitted to intensive care units (risk ratio 1.56; 95% CI, 1.31–1.87).[5] The risk for immunosuppression and susceptibility to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection varies between cancer types, treatments administered, and stages of therapy (e.g., patients who are actively being treated compared to those in remission). In a study that used data from the COVID-19 and Cancer Consortium Registry, cancer patients who were in remission or who had no evidence of disease were at a lower risk of death from COVID-19 than those who were receiving active treatment.[6] It is unclear whether cancer survivors are at increased risk for severe COVID-19 and its complications compared to people without a history of cancer.

Many organizations have outlined recommendations for treating patients with cancer during the COVID-19 pandemic, such as:

- National Comprehensive Cancer Network (NCCN)
- American Society of Hematology
- American Society of Clinical Oncology
- Society of Surgical Oncology
- American Society for Radiation Oncology
- International Lymphoma Radiation Oncology Group

This section of the COVID-19 Treatment Guidelines complements these sources and focuses on considerations regarding testing for SARS-CoV-2, management of COVID-19 in patients with cancer, and management of cancer-directed therapies during the COVID-19 pandemic. The optimal

management and therapeutic approach to COVID-19 in this population has not yet been defined.

Testing for COVID-19 in Patients With Cancer

The COVID-19 Treatment Guidelines Panel (the Panel) recommends molecular diagnostic testing for SARS-CoV-2 in patients with cancer who develop signs and symptoms of COVID-19 **(AIII)**.

Patients with cancer who are receiving chemotherapy are at risk of developing neutropenia. The NCCN *Guidelines for Hematopoietic Growth Factors* categorizes cancer treatment regimens based on the risk of developing neutropenia. A retrospective study suggests that cancer patients with neutropenia have a higher mortality rate if they develop COVID-19.[7] Due to the potential risk of poor clinical outcomes in the setting of neutropenia and/or during the perioperative period, the Panel recommends performing molecular diagnostic testing for SARS-CoV-2 prior to procedures that require anesthesia and before initiating cytotoxic chemotherapy and long-acting biologic therapy **(BIII)**.[8,9]

General Guidance on Medical Care for Cancer Patients During the COVID-19 Pandemic

Patients with cancer frequently engage with the health care system to receive treatment and supportive care for cancer and/or treatment-related complications. Telemedicine can minimize the need for in-person services and reduce the risk of SARS-CoV-2 exposure. The Centers for Disease Control and Prevention published a framework to help clinicians decide whether a patient should receive in-person or virtual care during the COVID-19 pandemic; this framework accounts for factors such as the potential harm of delayed care and the degree of SARS-CoV-2 transmission in a patient's community.[10] Telemedicine may improve access to providers for medically or socially vulnerable populations but could worsen disparities if these populations have limited access to technology. Nosocomial transmission of SARS-CoV-2 to patients and health care workers has been reported.[11-13] Principles of physical distancing and prevention strategies, including masking patients and health care workers and practicing hand hygiene, apply to all in-person interactions.[14]

Decisions about treatment regimens, surgery, and radiation therapy for the underlying malignancy should be made on an individual basis depending on the biology of the cancer, the need for hospitalization, the number of clinic visits required, and the anticipated degree of immunosuppression. Several key points should be considered:

- If possible, treatment delays should be avoided for curable cancers that have been shown to have worse outcomes when treatment is delayed (e.g., pediatric acute lymphoblastic leukemia).
- When deciding between equally effective treatment regimens, regimens that can be administered orally or those that require fewer infusions are preferred.[15,16]
- The potential risks of drug-related lung toxicity (e.g., from using bleomycin or PD1 inhibitors) must be balanced with the clinical efficacy of alternative regimens or the risk of delaying care.[17]
- Preventing neutropenia can decrease the risk of neutropenic fever and the need for emergency room evaluation and hospitalization during the COVID-19 pandemic. Granulocyte colony-stimulating factor (G-CSF) should be given with chemotherapy regimens that have intermediate (10% to 20%) or high (>20%) risks of febrile neutropenia.[18]
- Cancer treatment regimens that do not affect outcomes of COVID-19 in cancer patients may not need to be altered. In a prospective observational study, receipt of immunotherapy, hormonal therapy, or radiotherapy in the month prior to SARS-CoV-2 infection was not associated with an increased risk of mortality among cancer patients with COVID-19.[19] A retrospective study from Italy evaluated the incidence of SARS-CoV-2 infection in patients with prostate cancer and

found that 114 of 37,161 patients (0.3%) who were treated with therapies other than androgen deprivation therapy became infected, compared to four of 5,273 patients (0.08%) who were treated with androgen deprivation therapy (OR 4.05; 95% CI, 1.55–10.59). The viral spike proteins required for cell entry of SARS-CoV-2 are primed by TMPRSS2, an androgen-regulated gene. Whether androgen deprivation therapy protects against SARS-CoV-2 infection requires further investigation in larger cohorts.[20]

- Radiation therapy guidelines suggest increasing the dose per fraction and reducing the number of daily treatments in order to minimize the number of hospital visits during the COVID-19 pandemic.[15,16]

Blood supply shortages will likely continue during the COVID-19 pandemic due to social distancing, cancellation of blood drives, and infection among donors. Revised donor criteria have been proposed by the Food and Drug Administration to increase the number of eligible donors.[21] In patients with cancer, lowering the transfusion thresholds for blood products (e.g., red blood cells, platelets) in asymptomatic patients should be considered.[22,23] At this time, there is no evidence that COVID-19 can be transmitted through blood products.[24,25]

Febrile Neutropenia

Cancer patients with febrile neutropenia should undergo molecular diagnostic testing for SARS-CoV-2 and evaluation for other infectious agents; they should also be given empiric antibiotics, as outlined in the NCCN Guidelines.[26] Low-risk febrile neutropenia patients should be treated at home with oral antibiotics or intravenous infusions of antibiotics to limit nosocomial exposure to SARS-CoV-2. Patients with high-risk febrile neutropenia should be hospitalized per standard of care.[26] Empiric antibiotics should be continued per standard of care in patients who test positive for SARS-CoV-2. Clinicians should also continuously evaluate neutropenic patients for emergent infections.

Treating COVID-19 and Managing Chemotherapy in Patients With Cancer and COVID-19

Retrospective studies suggest that patients with cancer who were admitted to the hospital with SARS-CoV-2 infection have a high case fatality rate, with higher rates observed in patients with hematologic malignancies than in those with solid tumors.[27,28]

Recommendations for treatment of COVID-19 are the same for cancer patients as for the general population **(AIII)** (see Potential Antiviral Drugs Under Evaluation for the Treatment of COVID-19 and Immunomodulators Under Evaluation for the Treatment of COVID-19). Dexamethasone treatment in patients with COVID-19 who require supplemental oxygen or mechanical ventilation has been associated with a lower mortality rate.[29] In cancer patients, dexamethasone is commonly used to prevent chemotherapy-induced nausea, as a part of tumor-directed therapy, and to treat inflammation associated with brain metastasis. The side effects of using dexamethasone to treat SARS-CoV-2 are not anticipated to be different between patients with or without cancer. If possible, treatments that are not currently recommended for SARS-CoV-2 infection should be administered as part of a clinical trial, since the safety and efficacy of these agents have not been well defined in patients with cancer.

The NCCN recommends discontinuing G-CSF and granulocyte-macrophage colony-stimulating factor in patients with cancer and acute SARS-CoV-2 infection who do not have bacterial or fungal infections to avoid the hypothetical risk of increasing inflammatory cytokines and pulmonary inflammation.[18,30] Secondary infections (e.g., invasive pulmonary aspergillosis) have been reported in critically ill patients with COVID-19.[31,32]

Decisions about administering cancer-directed therapy to patients with acute COVID-19 and those who are recovering from COVID-19 should be made on a case-by-case basis; clinicians should consider the indication for chemotherapy, the goals of care, and the patient's history of tolerance to the treatment **(BIII)**. The optimal duration of time between resolution of infection and initiating or restarting cancer-directed therapy is unclear. Withholding treatment until COVID-19 symptoms have resolved is recommended, if possible. Prolonged viral shedding (detection of SARS-CoV-2 by molecular testing) may occur in cancer patients,[2] although it is unknown how this relates to infectious virus and how it impacts outcomes. Therefore, there is no role for repeat testing in those recovering from COVID-19, and the decision to restart cancer treatments in this setting should be made on a case-by-case basis. The Panel recommends that clinicians who are treating COVID-19 in patients with cancer consult with a hematologist or oncologist before adjusting cancer-directed medications **(AIII)**.

Medication Interactions

The use of potential antiviral or immune-based therapies to treat COVID-19 can present additional challenges in cancer patients. Clinicians should pay careful attention to potential drug-drug interactions and overlapping toxicities between drugs that are used to treat COVID-19 and cancer-directed therapies, prophylactic antimicrobials, corticosteroids, and other medications **(AIII)**.

Several anti-neoplastic medications have known interactions with therapies that are being investigated for COVID-19.[22] Tocilizumab can interact with vincristine and doxorubicin. Any COVID-19 therapy that may cause QT prolongation must be used with caution in patients treated with venetoclax, gilteritinib, and tyrosine kinase inhibitor therapy (e.g., nilotinib). Dexamethasone is commonly used as an antiemetic for cancer patients and is recommended for treatment of certain patients with COVID-19 (see Corticosteroids for more information). Dexamethasone is a weak to moderate cytochrome P450 (CYP) 3A4 inducer; therefore, interactions with any CYP3A4 substrates need to be considered. Lopinavir/ritonavir is a CYP3A4 inhibitor, and it can increase methotrexate, vincristine, or ruxolitinib concentrations. Lopinavir/ritonavir **is not recommended** for the treatment of COVID-19; however, patients may receive it in a clinical trial. In general, concomitant use of lopinavir/ritonavir and CYP3A4 substrates should be avoided. If lopinavir/ritonavir is used in combination with a cytotoxic drug that is also a 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 Immodulators 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 without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = 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 Immodulators Under Evaluation for Treatment of COVID-19 for more information. The medications that are used to treat COVID-19 may present different risks and benefits to transplant patients and nontransplant patients.

Assessment of SARS-CoV-2 Infection in Transplant and Cellular Therapy Candidates and Donors

The risk of transmission of SARS-CoV-2 from donors to candidates is unknown. The probability of donor or candidate infection with SARS-CoV-2 may be estimated by considering epidemiologic risk, obtaining clinical history, and testing with molecular techniques. No current testing strategy is sensitive enough or specific enough to totally exclude active infection. Living solid organ donors should be counseled on strategies to prevent infection and monitored for exposures and symptoms in the 14 days prior to scheduled transplant.[2] HCT donors should practice good hygiene and avoid crowded places and large group gatherings during the 28 days prior to donation.[3]

Assessment of Transplant and Cellular Therapy Candidates

Diagnostic molecular testing for SARS-CoV-2 is recommended for all potential SOT candidates with signs and symptoms that suggest acute COVID-19 infection **(AIII)**. All potential SOT candidates should be assessed for exposure to COVID-19 and clinical symptoms that are compatible with COVID-19 before they are called in for transplantation and should undergo diagnostic molecular testing for SARS-CoV-2 shortly before SOT in accordance with guidance from medical professional organizations **(AIII)**.

Clinicians should consider performing diagnostic testing for SARS-CoV-2 in all HCT and cellular therapy candidates who exhibit symptoms. All candidates should also undergo diagnostic molecular testing for SARS-CoV-2 shortly before HCT or cell therapy **(AIII)**.

Assessment of Donors

The COVID-19 Treatment Guidelines Panel (the Panel) recommends following the guidance from medical professional organizations and assessing all potential HCT donors for exposure to COVID-19 and clinical symptoms that are compatible with COVID-19 before donation **(AIII)**. Deceased donors should undergo screening for known symptoms and exposure to others with COVID-19 before transplantation, and decisions about using such organs should be made on a case-by-case basis **(BIII)**. Recommendations for screening are outlined in the ASTCT and EBMT guidelines.

If SARS-CoV-2 Infection Is Detected or Strongly Suspected

If SARS-CoV-2 is detected or if infection is strongly suspected in a potential SOT donor or candidate, transplant should be deferred, if possible **(BIII)**. The optimal disease-free interval before transplantation is not known. The risks of viral transmission should be balanced against the risks to the candidate, such as progression of the underlying disease and risk of mortality if the candidate does not receive the transplant. This decision should be continually reassessed as conditions evolve. For HCT and cellular therapy candidates, current guidelines recommend deferring transplants or immunotherapy procedures, including peripheral blood stem cell mobilization, bone marrow harvest, T cell collection, and conditioning/lymphodepletion in recipients who test positive for SARS-CoV-2 or who have clinical symptoms that are consistent with infection. Final decisions should be made on a case-by-case basis while weighing the risks of delaying or altering therapy for the underlying disease.

Transplant Recipients with COVID-19

SOT recipients who are receiving immunosuppressive therapy should be considered to be at increased risk for severe COVID-19.[1,4] A national survey of 88 U.S. transplant centers conducted between March 24 and 31, 2020, reported that 148 SOT recipients received a diagnosis of COVID-19 infection (69.6% were kidney recipients, 15.5% were liver recipients, 8.8% were heart recipients, and 6.1% were lung recipients).[5] COVID-19 was mild in 54% of recipients and moderate in 21% of recipients, and 25% of recipients were critically ill. Modification of immunosuppressive therapy during COVID-19 and the use of investigational therapies for treatment of COVID-19 varied widely among recipients. Initial reports of transplant recipients who were hospitalized with COVID-19 suggest mortality rates of up to 28%.[6-9]

Risk of Graft Rejection

There have been no published reports of graft rejection in SOT recipients who received a diagnosis of COVID-19, although this may be due to a limited ability to perform biopsies. Acute cellular rejection should not be presumed in SOT recipients without biopsy confirmation in individuals with or without COVID-19. Similarly, immunosuppressive therapy should be initiated in recipients with or without COVID-19 who have rejection confirmed by a biopsy.[1]

There is a lack of data on the incidence and clinical characteristics of SARS-CoV-2 infection in HCT and cellular therapy recipients. Experience with other respiratory viruses suggests that this population is at a high risk for severe disease, including increased rates of lower respiratory tract infection and mortality.[10] Factors that may determine clinical severity include degree of cytopenia, time since transplant, intensity of the conditioning regimen, graft source, degree of mismatch, and the need for further immunosuppression to manage graft-versus-host disease. For other respiratory viruses, HCT recipients often exhibit prolonged viral shedding,[11-14] which can have implications for infection prevention and for the timing of potential interventions.

Treatment of COVID-19 in Transplant Recipients

Currently, remdesivir, an antiviral agent, is the only drug approved by the Food and Drug Administration (FDA) for the treatment of COVID-19.

Preliminary data from a large randomized controlled trial have shown that a short course of dexamethasone (6 mg once daily for up to 10 days) can improve survival in patients with COVID-19 who are mechanically ventilated or who require supplemental oxygen.[15] At this time, the risks and benefits of using dexamethasone in transplant recipients with COVID-19 who are receiving immunosuppressive therapy, which may include corticosteroids, are unknown.

The Panel's recommendations for the use of remdesivir and dexamethasone in patients with COVID-19

can be found in the Therapeutic Management section.

A number of other investigational agents and drugs that are approved by the FDA for other indications are being evaluated for the treatment of COVID-19 (e.g., antiviral therapies, COVID-19 convalescent plasma) and its associated complications (e.g., immunomodulators, antithrombotic agents). In general, the considerations when treating COVID-19 are the same for transplant recipients as for the general population. When possible, treatment should be given as part of a clinical trial. The safety and efficacy of investigational agents and drugs that have been approved by the FDA for other indications are not well defined in transplant recipients. Moreover, it is unknown whether concomitant use of immunosuppressive agents to prevent allograft rejection in the setting of COVID-19 affects treatment outcome.

The use of antiviral or immune-based therapies for the treatment of COVID-19 can present additional challenges in transplant patients. Clinicians should pay special attention to the potential for drug-drug interactions and overlapping toxicities with concomitant medications, such as immunosuppressants that are used to prevent allograft rejection (e.g., corticosteroids, mycophenolate, and calcineurin inhibitors such as tacrolimus and cyclosporine), antimicrobials that are used to prevent opportunistic infections, and other medications. Dose modifications may be necessary for drugs that are used to treat COVID-19 in transplant recipients with pre-existing organ dysfunction. Adjustments to the immunosuppressive regimen should be individualized based on disease severity, the specific immunosuppressants used, the type of transplant, the time since transplantation, the drug concentration, and the risk of graft rejection.[7] Clinicians who are treating COVID-19 in transplant patients should consult with a transplant specialist before adjusting immunosuppressive medication **(AIII)**.

Certain therapeutics (e.g., remdesivir, tocilizumab) are associated with elevated levels of transaminases. For liver transplant recipients, the AASLD does not view abnormal liver biochemistries as a contraindication to using investigational or off-label therapeutics, although certain elevation thresholds may exclude patients from trials of some investigational agents.[16] Close monitoring of liver biochemistries is warranted in patients with COVID-19, especially when they are receiving agents with a known risk of hepatotoxicity.

Calcineurin inhibitors, which are commonly used to prevent allograft rejection, have a narrow therapeutic index. Medications that inhibit or induce cytochrome P450 enzymes or P-glycoprotein may put patients who receive calcineurin inhibitors at risk of clinically significant drug-drug interactions, increasing the need for therapeutic drug monitoring and the need to assess for signs of toxicity or rejection.[17] Similarly, transplant patients may be at a higher risk of adverse effects, particularly when their concomitant medications have overlapping toxicities. Specific concerns about the use of potential antiviral medications and immune-based therapy for COVID-19 in transplant patients are noted below. See Tables 2d and 4b for additional details.

Table 5. Special Concerns for Drugs That Are Being Evaluated for COVID-19 Treatment in Transplant Patients

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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 4b.
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.

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

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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 without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = 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 **(AIIb)**.   • Antiviral treatment of influenza can be stopped when influenza has been ruled out by nucleic acid detection assay in upper respiratory tract specimens for nonintubated patients and in both upper and lower respiratory tract specimens for intubated patients. • For influenza treatment in hospitalized and non-hospitalized patients, see the CDC and IDSA recommendations on antiviral treatment of influenza.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional **Rating of Evidence:** I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

Introduction

Influenza activity in the United States during the 2020–2021 influenza season is difficult to predict and could vary geographically and by the extent of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) community mitigation measures. During early 2020, sharp declines in influenza activity coincided with implementation of SARS-CoV-2 control measures in the United States and several Asian countries.[1-4] Very low influenza virus circulation was observed in Australia, Chile, and South Africa during the typical Southern Hemisphere influenza season in 2020.[5] Clinicians should monitor local influenza and SARS-CoV-2 activity (e.g., by tracking local and state public health surveillance data and testing performed at health care facilities) to inform evaluation and management of patients with acute respiratory illness.

Influenza Vaccination

There are no data on the safety, immunogenicity, or effectiveness of influenza vaccines in patients with mild COVID-19 or those who are recovering from COVID-19. Therefore, the optimal timing for influenza vaccination in these patients is unknown. The safety and efficacy of vaccinating persons who have mild illnesses from other etiologies have been documented.[6] On the basis of practice following other acute respiratory infections, the Panel recommends that persons with COVID-19 should receive an inactivated influenza vaccine **(BIII)**. The Centers for Disease Control and Prevention (CDC) has provided guidance on the timing of influenza vaccination for inpatients and outpatients with COVID-19 (see Interim Guidance for Routine and Influenza Immunization Services During the COVID-19 Pandemic). It is not known whether dexamethasone or other immunomodulatory therapies for COVID-19 will affect the immune response to influenza vaccine. However, despite this uncertainty, as long as influenza viruses are circulating, an unvaccinated person with COVID-19 should receive the influenza vaccine once they have substantially improved or recovered from COVID-19. See influenza vaccine recommendations from CDC and the Advisory Committee on Immunization Practices.

Clinical Presentation of Influenza Versus COVID-19

The signs and symptoms of uncomplicated, clinically mild influenza overlap with those of mild COVID-19. Ageusia and anosmia can occur with both diseases, but these symptoms are more common with COVID-19 than with influenza. Fever is not always present in patients with either disease, particularly in patients who are immunosuppressed or elderly. Complications of influenza and COVID-19 can be similar, but the onset of influenza complications and severe disease typically occurs within a week of illness onset whereas the onset of severe COVID-19 usually occurs in the second week of illness. Because of the overlap in signs and symptoms, when SARS-CoV-2 and influenza viruses are cocirculating, diagnostic testing for both viruses in people with an acute respiratory illness is needed to distinguish between SARS-CoV-2 and influenza virus, and to identify SARS-CoV-2 and influenza virus coinfection. Coinfection with influenza A or B viruses and SARS-CoV-2 has been described in case reports and case series,[7-11] but the frequency, severity, and risk factors for coinfection with these viruses versus for infection with either virus alone are unknown.

Which Patients Should be Tested for SARS-CoV-2 and influenza?

When influenza viruses and SARS-CoV-2 are cocirculating in the community, SARS-CoV-2 testing and influenza testing should be performed in all patients hospitalized with suspected COVID-19 or influenza (see Testing for SARS-CoV-2 Infection) **(AIII)**. When influenza viruses and SARS-CoV-2 are cocirculating in the community, SARS-CoV-2 testing should be performed in outpatients with suspected COVID-19, and influenza testing can be considered in outpatients with suspected influenza if the results will change clinical management of the illness **(BIII)**. Several multiplex assays that detect SARS-CoV-2 and influenza A and B viruses have received Food and Drug Administration Emergency Use Authorization and can provide results in 15 minutes to 8 hours on a single respiratory specimen.[12,13] For information on available influenza tests, including clinical algorithms for testing of patients when SARS-CoV-2 and influenza viruses are cocirculating, see the CDC Information for Clinicians on Influenza Virus Testing and recommendations of the Infectious Diseases Society of America (IDSA) on the use of influenza tests and interpretation of testing results.[14]

Which Patients Should Receive Antiviral Treatment of Influenza?

When SARS-CoV-2 and influenza viruses are cocirculating in the community, patients who require hospitalization and are suspected of having either or both viral infections should receive influenza antiviral treatment with oseltamivir as soon as possible without waiting for influenza testing results

(AIIb).[14] Treatment for influenza is the same for all patients regardless of SARS-CoV-2 coinfection **(AIII)**. See the CDC Influenza Antiviral Medications: Summary for Clinicians, including clinical algorithms for antiviral treatment of patients with suspected or confirmed influenza when SARS-CoV-2 and influenza viruses are cocirculating, and the IDSA Clinical Practice Guidelines recommendations on antiviral treatment of influenza.

If a diagnosis of COVID-19 or another etiology is confirmed and if the result of an influenza nucleic acid detection assay from an upper respiratory tract specimen is negative:

- *In a Patient Who is Not Intubated:* Antiviral treatment for influenza can be stopped.
- *In a Patient Who is Intubated:* Antiviral treatment for influenza should be continued and if a lower respiratory tract specimen (e.g., endotracheal aspirate) can be safely obtained, it should be tested by influenza nucleic acid detection. If the lower respiratory tract specimen is also negative, influenza antiviral treatment can be stopped.

Treatment Considerations for Hospitalized Patients With Suspected or Confirmed SARS-CoV-2 and Influenza Virus Coinfection

- Corticosteroids, which may be used for the treatment of COVID-19, may prolong influenza viral replication and viral RNA detection and may be associated with poor outcomes.[14,15]
- Oseltamivir has no activity against SARS-CoV-2.[16] Oseltamivir does not have any known interactions with remdesivir.
- Standard-dose oseltamivir is well absorbed even in critically ill patients. For patients who cannot tolerate oral or enterically administered oseltamivir (e.g., because of gastric stasis, malabsorption, or gastrointestinal bleeding), intravenous peramivir is an option.[14] There are no data on peramivir activity against SARS-CoV-2.
- CDC does not recommend inhaled zanamivir and oral baloxavir for the treatment of influenza in hospitalized patients because of insufficient safety and efficacy data (see the CDC Influenza Antiviral Medications: Summary for Clinicians). There are no data on zanamivir activity against SARS-CoV-2. Baloxavir has no activity against SARS-CoV-2.[16]
- Based upon limited data, the co-occurrence of community-acquired secondary bacterial pneumonia with COVID-19 appears to be infrequent and may be more common with influenza.[17,18] Typical bacterial causes of community-acquired pneumonia with severe influenza are *Staphylococcus aureus* (methicillin-resistant *S. aureus* [MRSA] and methicillin-susceptible *S. aureus* [MSSA]), *Streptococcus pneumoniae*, and group A *Streptococcus*.[14]
- Patients with COVID-19 who develop new respiratory symptoms with or without fever or respiratory distress, and without a clear diagnosis, should be evaluated for the possibility of nosocomial influenza.

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

Last Updated: February 11, 2021

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Community Members	
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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: February 11, 2021

Reporting Period: October 1, 2019, to September 30, 2020

Panel Member	Financial Disclosure	
	Company	Relationship
Judith Aberg, MD	Atea Pharmaceuticals	Research Support
	Emergent BioSolutions	Research Support
	Gilead Sciences	Research Support
	Pfizer	Research Support
	Regeneron	Research Support
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	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
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Laura Bosque Ortiz, BS	None	N/A
John T. Brooks, MD	None	N/A
Timothy Burgess, MD	None	N/A
Danielle M. Campbell, MPH	ViiV Healthcare	Summit Attendee
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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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Susan L. Davis, PharmD	Merck & Co.	Honoraria
Laurie K. Doepel, BA	None	N/A
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Panel Member	Financial Disclosure	
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Rajesh Gandhi, MD	None	N/A
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	Merck & Co.	Advisory Board
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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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
Virginia Sheikh, MD, MHS	None	N/A
Steven Q. Simpson, MD	None	N/A
Kanal Singh, MD, MPH	None	N/A

Panel Member	Financial Disclosure	
	Company	Relationship
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Phyllis Tien, MD, MSc	Merck & Co.	Research Support
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	Ansun BioPharma	Research Support
	Kyorin Pharmaceutical Co.	Advisory Board
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	Eli Lilly and Company	Consultant
	Pfizer	Consultant
Philip Zachariah, MD, MSc	Merck & Co.	Research Support

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 **(AIIb)**.   • Antiviral treatment of influenza can be stopped when influenza has been ruled out by nucleic acid detection assay in upper respiratory tract specimens for nonintubated patients and in both upper and lower respiratory tract specimens for intubated patients. • For influenza treatment in hospitalized and non-hospitalized patients, see the CDC and IDSA recommendations on antiviral treatment of influenza.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional **Rating of Evidence:** I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

Introduction

Influenza activity in the United States during the 2020–2021 influenza season is difficult to predict and could vary geographically and by the extent of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) community mitigation measures. During early 2020, sharp declines in influenza activity coincided with implementation of SARS-CoV-2 control measures in the United States and several Asian countries.[1-4] Very low influenza virus circulation was observed in Australia, Chile, and South Africa during the typical Southern Hemisphere influenza season in 2020.[5] Clinicians should monitor local influenza and SARS-CoV-2 activity (e.g., by tracking local and state public health surveillance data and testing performed at health care facilities) to inform evaluation and management of patients with acute respiratory illness.

Influenza Vaccination

There are no data on the safety, immunogenicity, or effectiveness of influenza vaccines in patients with mild COVID-19 or those who are recovering from COVID-19. Therefore, the optimal timing for influenza vaccination in these patients is unknown. The safety and efficacy of vaccinating persons who have mild illnesses from other etiologies have been documented.[6] On the basis of practice following other acute respiratory infections, the Panel recommends that persons with COVID-19 should receive an inactivated influenza vaccine **(BIII)**. The Centers for Disease Control and Prevention (CDC) has provided guidance on the timing of influenza vaccination for inpatients and outpatients with COVID-19 (see Interim Guidance for Routine and Influenza Immunization Services During the COVID-19 Pandemic). It is not known whether dexamethasone or other immunomodulatory therapies for COVID-19 will affect the immune response to influenza vaccine. However, despite this uncertainty, as long as influenza viruses are circulating, an unvaccinated person with COVID-19 should receive the influenza vaccine once they have substantially improved or recovered from COVID-19. See influenza vaccine recommendations from CDC and the Advisory Committee on Immunization Practices.

Clinical Presentation of Influenza Versus COVID-19

The signs and symptoms of uncomplicated, clinically mild influenza overlap with those of mild COVID-19. Ageusia and anosmia can occur with both diseases, but these symptoms are more common with COVID-19 than with influenza. Fever is not always present in patients with either disease, particularly in patients who are immunosuppressed or elderly. Complications of influenza and COVID-19 can be similar, but the onset of influenza complications and severe disease typically occurs within a week of illness onset whereas the onset of severe COVID-19 usually occurs in the second week of illness. Because of the overlap in signs and symptoms, when SARS-CoV-2 and influenza viruses are cocirculating, diagnostic testing for both viruses in people with an acute respiratory illness is needed to distinguish between SARS-CoV-2 and influenza virus, and to identify SARS-CoV-2 and influenza virus coinfection. Coinfection with influenza A or B viruses and SARS-CoV-2 has been described in case reports and case series,[7-11] but the frequency, severity, and risk factors for coinfection with these viruses versus for infection with either virus alone are unknown.

Which Patients Should be Tested for SARS-CoV-2 and influenza?

When influenza viruses and SARS-CoV-2 are cocirculating in the community, SARS-CoV-2 testing and influenza testing should be performed in all patients hospitalized with suspected COVID-19 or influenza (see Testing for SARS-CoV-2 Infection) **(AIII)**. When influenza viruses and SARS-CoV-2 are cocirculating in the community, SARS-CoV-2 testing should be performed in outpatients with suspected COVID-19, and influenza testing can be considered in outpatients with suspected influenza if the results will change clinical management of the illness **(BIII)**. Several multiplex assays that detect SARS-CoV-2 and influenza A and B viruses have received Food and Drug Administration Emergency Use Authorization and can provide results in 15 minutes to 8 hours on a single respiratory specimen.[12,13] For information on available influenza tests, including clinical algorithms for testing of patients when SARS-CoV-2 and influenza viruses are cocirculating, see the CDC Information for Clinicians on Influenza Virus Testing and recommendations of the Infectious Diseases Society of America (IDSA) on the use of influenza tests and interpretation of testing results.[14]

Which Patients Should Receive Antiviral Treatment of Influenza?

When SARS-CoV-2 and influenza viruses are cocirculating in the community, patients who require hospitalization and are suspected of having either or both viral infections should receive influenza antiviral treatment with oseltamivir as soon as possible without waiting for influenza testing results

(AIIb).[14] Treatment for influenza is the same for all patients regardless of SARS-CoV-2 coinfection **(AIII)**. See the CDC Influenza Antiviral Medications: Summary for Clinicians, including clinical algorithms for antiviral treatment of patients with suspected or confirmed influenza when SARS-CoV-2 and influenza viruses are cocirculating, and the IDSA Clinical Practice Guidelines recommendations on antiviral treatment of influenza.

If a diagnosis of COVID-19 or another etiology is confirmed and if the result of an influenza nucleic acid detection assay from an upper respiratory tract specimen is negative:

- *In a Patient Who is Not Intubated:* Antiviral treatment for influenza can be stopped.
- *In a Patient Who is Intubated:* Antiviral treatment for influenza should be continued and if a lower respiratory tract specimen (e.g., endotracheal aspirate) can be safely obtained, it should be tested by influenza nucleic acid detection. If the lower respiratory tract specimen is also negative, influenza antiviral treatment can be stopped.

Treatment Considerations for Hospitalized Patients With Suspected or Confirmed SARS-CoV-2 and Influenza Virus Coinfection

- Corticosteroids, which may be used for the treatment of COVID-19, may prolong influenza viral replication and viral RNA detection and may be associated with poor outcomes.[14,15]
- Oseltamivir has no activity against SARS-CoV-2.[16] Oseltamivir does not have any known interactions with remdesivir.
- Standard-dose oseltamivir is well absorbed even in critically ill patients. For patients who cannot tolerate oral or enterically administered oseltamivir (e.g., because of gastric stasis, malabsorption, or gastrointestinal bleeding), intravenous peramivir is an option.[14] There are no data on peramivir activity against SARS-CoV-2.
- CDC does not recommend inhaled zanamivir and oral baloxavir for the treatment of influenza in hospitalized patients because of insufficient safety and efficacy data (see the CDC Influenza Antiviral Medications: Summary for Clinicians). There are no data on zanamivir activity against SARS-CoV-2. Baloxavir has no activity against SARS-CoV-2.[16]
- Based upon limited data, the co-occurrence of community-acquired secondary bacterial pneumonia with COVID-19 appears to be infrequent and may be more common with influenza.[17,18] Typical bacterial causes of community-acquired pneumonia with severe influenza are *Staphylococcus aureus* (methicillin-resistant *S. aureus* [MRSA] and methicillin-susceptible *S. aureus* [MSSA]), *Streptococcus pneumoniae*, and group A *Streptococcus*.[14]
- Patients with COVID-19 who develop new respiratory symptoms with or without fever or respiratory distress, and without a clear diagnosis, should be evaluated for the possibility of nosocomial influenza.

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

Last Updated: February 11, 2021

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Community Members	
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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: February 11, 2021

Reporting Period: October 1, 2019, to September 30, 2020

Panel Member	Financial Disclosure	
	Company	**Relationship**
Judith Aberg, MD	Atea Pharmaceuticals	Research Support
	Emergent BioSolutions	Research Support
	Gilead Sciences	Research Support
	Pfizer	Research Support
	Regeneron	Research Support
Adaora Adimora, MD, MPH	Gilead Sciences	Research Support
	Merck & Co.	Advisory Board, Consultant
Jason Baker, MD, MS	Gilead Sciences	Research Support
	Humanigen	Research Support
Lisa Baumann Kreuziger, MD, MS	3M	Stockholder, Spouse Is Employee
	Quercegen Pharmaceuticals	Advisory Board for Nonapproved Medications
	Versiti	Employee
Roger Bedimo, MD, MS	Gilead Sciences	Advisory Board
	Merck & Co.	Advisory Board
	ViiV Healthcare	Advisory Board, Research Support
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John T. Brooks, MD	None	N/A
Timothy Burgess, MD	None	N/A
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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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Robert W. Eisinger, PhD	None	N/A

Panel Member	Financial Disclosure	
	Company	Relationship
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Joseph Francis, MD, MPH	None	N/A
John J. Gallagher, DNP, RN	Medtronic	Consultant
Rajesh Gandhi, MD	None	N/A
David V. Glidden, PhD	Gilead Sciences	Consultant
	Merck & Co.	Advisory Board
Birgit Grund, PhD	None	N/A
Roy M. Gulick, MD, MPH	None	N/A
Alison Han, MD	None	N/A
Erica J. Hardy, MD, MMSc	None	N/A
Carly Harrison	AstraZeneca	Advisory Board
	Aurinia Pharmaceuticals	Advisory Board, Stockholder
Elizabeth S. Higgs, MD, DTM&H, MIA	None	N/A
Carl Hinkson, MSRC	None	N/A
Brenna L. Hughes, MD, MSc	Merck & Co.	Advisory Board
Steven Johnson, MD	ViiV Healthcare	Advisory Board
Marla J. Keller, MD	None	N/A
Arthur Kim, MD	None	N/A
Safia Kuriakose, PharmD	None	N/A
H. Clifford Lane, MD	None	N/A
Jeffrey L. Lennox, MD	None	N/A
Andrea M. Lerner, MD, MS	None	N/A
Mitchell M. Levy, MD	Inotrem	Research Support
Gregory Martin, MD, MSc	Beckman Coulter	Consultant
	Genentech	Data and Safety Monitoring Board Chair/Member
	Regeneron	Consultant
Henry Masur, MD	None	N/A
Susanna Naggie, MD, MHS	AbbVie	Research Support
	Gilead Sciences	Research Support
	Vir Biotechnology	Advisory Board, Stockholder
Martha C. Nason, PhD	Bristol-Myers Squibb Company	Stockholder
	Medtronic	Stockholder
Alice K. Pau, PharmD	None	N/A
Andrew T. Pavia, MD	GlaxoSmithKline	Consultant (related to influenza)
Nitin Seam, MD	None	N/A
Virginia Sheikh, MD, MHS	None	N/A
Steven Q. Simpson, MD	None	N/A
Kanal Singh, MD, MPH	None	N/A

Panel Member	Financial Disclosure	
	Company	Relationship
Susan Swindells, MBBS	ViiV Healthcare	Research Support
Pablo Tebas, MD	Inovio Pharmaceuticals	Research Support
Phyllis Tien, MD, MSc	Merck & Co.	Research Support
Timothy M. Uyeki, MD, MPH	None	N/A
Alpana A. Waghmare, MD	AlloVir	Research Support
	Ansun BioPharma	Research Support
	Kyorin Pharmaceutical Co.	Advisory Board
Robert Walker, MD	None	N/A
Kevin C. Wilson, MD	None	N/A
Jinoos Yazdany, MD, MPH	AstraZeneca	Consultant, Research Support
	Eli Lilly and Company	Consultant
	Pfizer	Consultant
Philip Zachariah, MD, MSc	Merck & Co.	Research Support