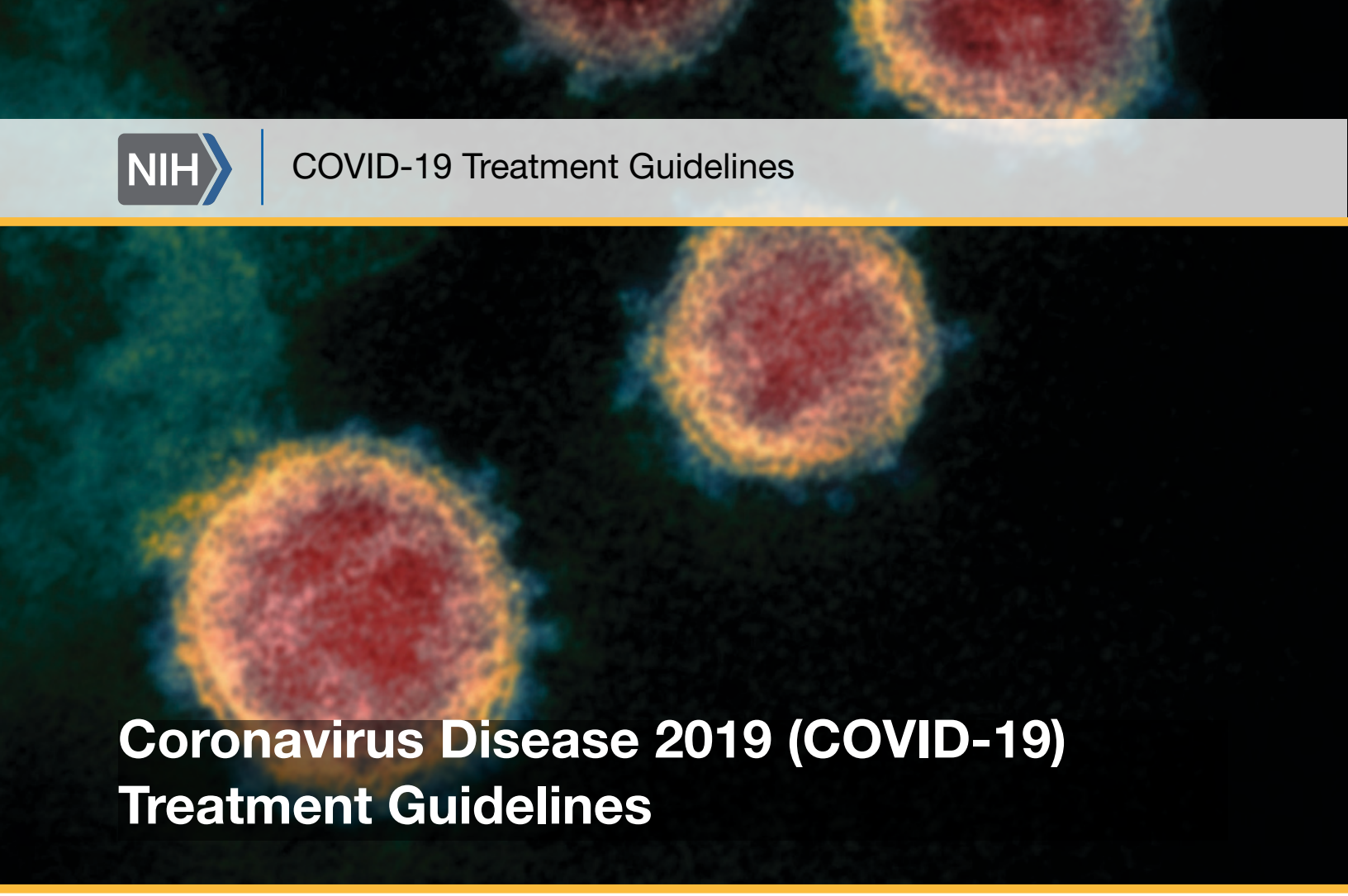

Coronavirus Disease 2019 (COVID-19) Treatment Guidelines

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How to Cite the COVID-19 Treatment Guidelines:

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

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

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What's New in the Guidelines

Last Updated: May 31, 2022

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 Guidelines Development for additional details on the development process).

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

May 31, 2022

Critical Care for Children

Four new sections were added to the Guidelines to discuss the unique aspects of managing critically ill children with COVID-19 or multisystem inflammatory syndrome in children (MIS-C). The new sections are:

- Introduction to Critical Care Management of Children With COVID-19
- Extracorporeal Membrane Oxygenation for Children
- Hemodynamic Considerations for Children
- Oxygenation and Ventilation for Children

Antithrombotic Therapy in Patients With COVID-19

Since the last update, the results from several large randomized controlled trials that evaluated the use of antiplatelet therapy in hospitalized patients with COVID-19 have been published. Additionally, a randomized controlled trial evaluated a 35-day course of rivaroxaban after hospital discharge in patients with COVID-19 who were at risk of experiencing thromboembolic events.

After reviewing the results of these studies, the Panel provides the following recommendations:

- The Panel **recommends against** the use of antiplatelet therapy to prevent COVID-19 progression or death in noncritically ill patients **(BIIa)**.
- There is insufficient evidence for the Panel to recommend either for or against antiplatelet therapy in critically ill patients with COVID-19.
- The Panel **recommends against** routinely continuing venous thromboembolism (VTE) prophylaxis for patients with COVID-19 after hospital discharge, except in a clinical trial **(AIII)**.
- For patients who are at high risk for VTE and low risk for bleeding, there is insufficient evidence to recommend either for or against continuing anticoagulation after hospital discharge unless another indication for VTE prophylaxis exists.

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The rationale for the Panel's recommendations is discussed in this section. A new table summarizes the data from randomized controlled trials that evaluated the use of antiplatelet therapy in hospitalized patients with COVID-19.

Critical Care for Adults

The Panel made a number of updates to these sections, including:

- The rationale in Oxygenation and Ventilation for Adults was revised to include data from recent clinical trials.
- The Panel updated the recommendations and rationale for empiric broad-spectrum antibiotics in Pharmacologic Interventions for Critically Ill Patients.
- The Infection Control and Acute Kidney Injury and Renal Replacement Therapy sections have been archived.

Corticosteroids

The rationale in this section and the information in Table 4a incorporate new data from clinical trials, including trials that investigated different doses of dexamethasone for the treatment of COVID-19.

Colchicine

This section includes results from the COLCOVID trial, an open-label, multicenter, randomized trial that evaluated the use of colchicine in hospitalized adults with COVID-19. After reviewing the results of the trial, the Panel continues to **recommend against** the use of colchicine for the treatment of hospitalized patients with COVID-19 **(AI)**.

Special Considerations in Adults and Children With Cancer

The Panel updated the information on the use of COVID-19 vaccines in patients with cancer and their close contacts. This section also discusses using tixagevimab plus cilgavimab (Evusheld) as pre-exposure prophylaxis (PrEP) in these patients and the potential drug-drug interactions between ritonavir-boosted nirmatrelvir (Paxlovid) and certain chemotherapeutic agents.

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

The Panel added COVID-19 vaccination recommendations for potential organ and stem cell donors, and for close contacts of transplant and cellular immunotherapy candidates and recipients. This section also discusses using tixagevimab plus cilgavimab as PrEP in transplant candidates and recipients and the potential drug-drug interactions between ritonavir-boosted nirmatrelvir and certain immunosuppressants that are used in these patients.

May 13, 2022

Ritonavir-Boosted Nirmatrelvir (Paxlovid)

The guidance on identifying and managing drug-drug interactions has moved to a new section of the Guidelines, entitled Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications. The Ritonavir-Boosted Nirmatrelvir (Paxlovid) section retains the general description of ritonavir-boosted nirmatrelvir, the Panel's recommendations for using this regimen, and a discussion of the clinical data that support those recommendations.

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This section has been updated to acknowledge reports of SARS-CoV-2 viral rebound and the recurrence of COVID-19 symptoms in patients who completed a 5-day course of ritonavir-boosted nirmatrelvir. The frequency and clinical implications of these events are not yet known.

Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications

Many commonly used medications can be safely coadministered with ritonavir-boosted nirmatrelvir despite its drug-drug interaction potential. In some cases, however, drug-drug interactions with ritonavir-boosted nirmatrelvir may lead to serious or life-threatening drug toxicities. This new section highlights the importance of evaluating a patient's medication regimen for potential drug-drug interactions before prescribing ritonavir-boosted nirmatrelvir. However, because ritonavir-boosted nirmatrelvir is the only highly effective oral antiviral for the treatment of COVID-19, drug-drug interactions that can be safely managed **should not preclude** the use of this regimen.

The section provides guidance on management strategies and a variety of resources that clinicians can use to identify potential interactions between ritonavir-boosted nirmatrelvir and concomitant medications.

This section also includes 2 quick reference lists:

- Box 1 lists examples of commonly prescribed medications that can be safely coadministered with ritonavir-boosted nirmatrelvir.
- Box 2 lists medications with clinically significant interactions with ritonavir-boosted nirmatrelvir. The list is divided into categories of medications that:
  - Should not be coadministered with ritonavir-boosted nirmatrelvir;
  - Can be withheld temporarily, if clinically appropriate;
  - May be continued with dose adjustments, if clinically appropriate; *or*
  - May be continued while the patient is monitored for adverse effects.

Prioritization of Anti-SARS-CoV-2 Therapies for the Treatment and Prevention of COVID-19 When There Are Logistical or Supply Constraints

The Panel updated this section to highlight that this prioritization guidance should be used **ONLY** when logistical or supply constraints limit the availability of therapies. The Panel emphasizes that when there are no supply or logistical constraints, therapies for the prevention or treatment of SARS-CoV-2 infection can be prescribed for any eligible individual as recommended in these Guidelines.

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Guidelines Development

Last Updated: April 29, 2022

The COVID-19 Treatment Guidelines were 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 are updated frequently to reflect newly published data and other authoritative information.

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 the development of treatment guidelines. Panel members include representatives from federal agencies, health care organizations, 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 Clinical Pharmacy
- 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

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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 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 voting members; this applies to recommendations for and against treatments and cases where there is insufficient evidence 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 that are evaluated 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. During this process, the Panel evaluates the data, including the source of the data, the type of study (e.g., randomized controlled trial, prospective or retrospective cohort study, case series, in vitro study), 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 2 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.

Table 1. Recommendation Rating Scheme

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

To develop the recommendations in these Guidelines, the Panel uses data from the rapidly growing body of research on COVID-19. The Panel also relies heavily on experience with other diseases, supplemented with the 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 that the potential benefits of using this intervention outweigh the potential risks.
- **There is insufficient evidence 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 when there are currently not enough data to support a recommendation, or the available data are conflicting.
- **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 in treating COVID-19.

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

Evolving Knowledge on Treatments for COVID-19

Remdesivir, an antiviral agent, is currently the only drug that is approved by the Food and Drug Administration for the treatment of COVID-19. An array of drugs that are 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, Emergency Investigational New Drug 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.

New data on the treatment of COVID-19 are emerging at a rapid pace. Some of these data are being published in peer-reviewed journals, but some can be found in manuscripts that have not yet been peer reviewed or in 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.

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Overview of COVID-19

Last Updated: April 29, 2022

Epidemiology

The COVID-19 pandemic has exploded since cases were first reported in China in December 2019. As of April 15, 2022, more than 503 million cases of COVID-19—caused by SARS-CoV-2 infection—have been reported globally, including more than 6.2 million deaths.[1]

Individuals of all ages are at risk for SARS-CoV-2 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 of COVID-19 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.[2] The percentage of patients who died was 12 times higher among those with reported medical conditions (19.5%) than among those without medical conditions (1.6%), and the percentage of patients who were hospitalized was 6 times higher among those with reported medical conditions (45.4%) than among those without medical conditions (7.6%). Mortality was highest in patients aged >70 years, regardless of the presence of chronic medical conditions. Data on comorbid health conditions among patients with COVID-19 indicate that 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, liver disease (especially in patients with cirrhosis), obesity, sickle cell disease, and other immunocompromising conditions. Transplant recipients and pregnant people are also at a higher risk of severe COVID-19.[3-10]

Data from the United States suggest that racial and ethnic minorities experience higher rates of COVID-19, 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.[4,16] 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 increase the risk of developing severe COVID-19.[15]

SARS-CoV-2 Variants

Like other RNA viruses, SARS-CoV-2 is constantly evolving through random mutations. New mutations can potentially increase or decrease infectiousness and virulence. In addition, mutations can increase the virus' ability to evade adaptive immune responses from past SARS-CoV-2 infection or vaccination. This viral evolution may increase the risk of reinfection or decrease the efficacy of vaccines.[18] There is evidence that some SARS-CoV-2 variants have reduced susceptibility to plasma from people who were previously infected or immunized, as well as to certain monoclonal antibodies (mAbs) that are being considered for prevention and treatment.[19-21]

Since December 2020, the World Health Organization (WHO) has assigned Greek letter designations to several identified variants. A SARS-CoV-2 variant designated as a variant of concern (VOC) displays certain characteristics, such as increased transmissibility or virulence. In addition, vaccines and therapeutics may have decreased effectiveness against VOCs, and the mutations found in these variants

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may interfere with the targets of diagnostic tests. The variant of interest (VOI) designation has been used for important variants that are not fully characterized; however, organizations do not use the same variant designations, and they may define their variant designations differently.[22,23] In September 2021, the Centers for Disease Control and Prevention (CDC) added a new designation for variants: variant being monitored (VBM). This refers to variants for which data indicate a potential or clear impact on approved or authorized medical countermeasures or variants associated with more severe disease or increased transmission rates. However, these variants are either no longer detected or are circulating at very low levels in the United States; therefore, they do not pose a significant and imminent risk to public health in the United States.

The Omicron (B.1.1.529) variant was designated a VOC in November 2021 and rapidly became the dominant variant across the globe. More recently, the Omicron subvariants BA.1, BA.1.1, and BA.2 have emerged. The Omicron VOC is more transmissible than other variants and is not susceptible to some of the anti-SARS-CoV-2 mAbs that have been developed for treatment and prevention.[20,21,24] The Omicron VOC has surpassed Delta (B.1.617.2) as the dominant variant in the United States; the Delta variant was first identified in India and was the dominant variant in July 2021.

Earlier variants include the Alpha (B.1.1.7) variant, which was first seen in the United Kingdom and has been shown to be highly infectious and possibly more virulent than previously reported variants;[25-27] the Beta (B.1.351) variant, which was originally identified in South Africa; and the Gamma (P.1) variant, which was identified in Manaus, Brazil. The Beta and Gamma variants demonstrated reduced susceptibility to select anti-SARS-CoV-2 mAbs used for treatment and prevention. Although the Alpha, Beta, and Gamma variants were previously designated as VOCs, they have largely disappeared worldwide. For a detailed discussion on the susceptibility of certain VOCs, VOIs, and VBMs to available anti-SARS-CoV-2 mAbs, please see Anti-SARS-CoV-2 Monoclonal Antibodies.

Data on the emergence, transmission, and clinical relevance of these new variants are rapidly evolving; this is especially true for research on how variants might affect transmission rates, disease progression, vaccine development, and the efficacy of current therapeutics. Because the research on variants is moving quickly and the classification of the different variants may change over time, websites such as the CDC COVID Data Tracker and CoVariants.org provide regular updates on the data for SARS-CoV-2 variants. The COVID-19 Treatment Guidelines Panel reviews emerging data on these variants, paying particular attention to research on the impacts of these variants on testing, prevention, and treatment.

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.[6,28,29] The spectrum of illness can range from asymptomatic infection to severe pneumonia with acute respiratory distress syndrome and death. Among 72,314 people 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, oxygen saturation ≤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 multiple organ dysfunction syndrome or failure).[30] 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.[2] 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 of patients with COVID-19 vary, but bilateral multifocal opacities are the most common. The abnormalities seen in computed tomography of the chest also

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vary, but the most common are bilateral peripheral ground-glass opacities, with areas of consolidation developing later in the clinical course of COVID-19.[31] Imaging may be normal early in infection and can be abnormal in the absence of symptoms.

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.

Although COVID-19 is primarily a pulmonary disease, emerging data suggest that it also leads to cardiac,[32,33] dermatologic,[34] hematologic,[35] hepatic,[36] neurologic,[37,38] renal,[39,40] and other complications. Thromboembolic events also occur in patients with COVID-19, with the highest risk occurring in critically ill patients.[41]

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).[42,43] Please see Special Considerations in Children for more information.

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Testing for SARS-CoV-2 Infection

Last Updated: March 24, 2022

Summary Recommendations

• 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 mid-turbinate, anterior nasal, or oropharyngeal) to diagnose acute infection of SARS-CoV-2; if it is not practical to use a NAAT or if NAATs are not available, an antigen test may be used **(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)**.
• A NAAT should not be repeated in an asymptomatic person (with the exception of health care workers) within 90 days of a previous SARS-CoV-2 infection, even if the person has had a significant exposure to SARS-CoV-2 **(AIII)**.
• SARS-CoV-2 reinfection has been reported in people after an initial diagnosis of the infection; therefore, clinicians should consider using a NAAT for those who have recovered from a previous infection and who present with symptoms that are compatible with SARS-CoV-2 infection if there is no 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)**.
• There is insufficient evidence for the Panel to recommend either for or against the use of SARS-CoV-2 serologic testing to assess for immunity or to guide clinical decisions about using COVID-19 vaccines or anti-SARS-CoV-2 monoclonal antibodies in certain people.

Rating of Recommendations: A = Strong; B = Moderate; C = Weak **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

Diagnostic Testing for SARS-CoV-2 Infection

Everyone who has symptoms that are consistent with COVID-19 and people with known high-risk exposures to 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. Testing may also be used for screening, determining the length of a patient's isolation period, and other nondiagnostic purposes.[1]

A number of diagnostic tests for SARS-CoV-2 infection (e.g., NAATs, antigen tests) have received Emergency Use Authorizations (EUAs) from the Food and Drug Administration (FDA),[2] but no diagnostic test has been approved by the FDA. Diagnostic tests have been authorized for use by trained personnel in several settings, including lab facilities. They can also be used in point-of-care settings, where the test is performed by trained personnel at or near the place where the specimen was collected. Point-of-care settings include physician offices, pharmacies, long-term care facilities, and school clinics.

Antigen tests can be self-administered, and most can be used in point-of-care settings, allowing results to be available within minutes. Some NAATs can also be self-administered at home or in other non-health care locations and shipped to a laboratory for testing.

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.[3] Lower respiratory tract samples have a higher yield than upper respiratory tract samples, but they

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are often not obtained because of concerns about aerosolization of the virus during sample collection procedures. Some of the tests that have received EUAs can also be performed on saliva specimens, but the quality of saliva specimens can be highly variable. Studies are currently evaluating the use of other sample types, including stool samples.

Nucleic Acid Amplification Testing for SARS-CoV-2 Infection

Reverse transcription 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 isothermal amplification platforms (e.g., nicking endonuclease amplification reaction [NEAR], loop-mediated isothermal amplification [LAMP], transcription-mediated amplification [TMA]).[4] Some NAATs have also received EUAs for use in different settings, such as in laboratory facilities and point-of-care settings. Laboratory-based NAATs generally have higher sensitivity than point-of-care tests.[4]

Clinically, there may be a window period of up to 5 days after exposure before viral nucleic acids can be detected. Diagnostically, some NAATs may produce false negative results if a mutation occurs in the part of the virus' genome that is assessed by that test.[5] The FDA monitors the potential effects of SARS-CoV-2 genetic variations on NAAT results and issues updates when specific variations could affect the performance of NAATs that have received EUAs. Generally, false negative results are more likely to occur when using NAATs that rely on only 1 genetic target. Therefore, a single negative test result does not exclude the possibility of SARS-CoV-2 infection in people who have a high likelihood of infection based on their exposure history and/or their clinical presentation.[6]

Many commercial NAATs that use RT-PCR rely on multiple targets to detect the virus, such that even if a mutation impacts 1 of the targets, the other RT-PCR targets will still work.[7] NAATs that use multiple targets are less likely to be impacted by an increased prevalence of genetic variants. In fact, because each of these tests target multiple locations on the virus' genome, they can be helpful in identifying new genetic variants before they become widespread in the population. For example, the B.1.1.7 (Alpha) variant and the BA.1 subvariant of the B.1.1.529 (Omicron) variant, both of which have been associated with increased transmission, carry many mutations, including a double deletion at positions 69 and 70 on the spike protein gene (S-gene). This mutation appears to impact the detection of the S-gene but does not impact other genetic targets in certain NAATs. If COVID-19 is still suspected after a patient receives a negative test result, clinicians should consider repeating testing; ideally, they should use a NAAT with different genetic targets.[5]

SARS-CoV-2 poses several diagnostic challenges, including the potential for discordant viral shedding between the upper and lower respiratory tract. However, due to the high specificity of NAATs, 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.[8-13] For intubated or mechanically ventilated patients with clinical signs and symptoms that are 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 carefully considering the risk of exposing staff to infectious aerosols. Endotracheal aspiration appears to

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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

NAATs can detect SARS-CoV-2 RNA in specimens obtained weeks to months after the onset of COVID-19 symptoms.[14,15] 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.[16,17] Furthermore, both virologic studies and contact tracing of high-risk contacts show a low risk for SARS-CoV-2 transmission after these intervals.[18,19] Based on these results, the Centers for Disease Control and Prevention (CDC) recommends that NAATs should not be repeated in asymptomatic persons within 90 days of a previous SARS-CoV-2 infection, even if the person has had a significant exposure to SARS-CoV-2.[20] An exception to this is for health care workers who meet the specific criteria found in CDC guidance.[21] If there are concerns that an immunocompromised health care worker may still be infectious >20 days from the onset of SARS-CoV-2 infection, consulting local employee health services about return-to-work testing policies is advised.

SARS-CoV-2 reinfection has been reported in people after an initial diagnosis of infection; therefore, clinicians should consider using a NAAT for those who have recovered from a previous infection and who present with symptoms that are compatible with SARS-CoV-2 infection if there is no alternative diagnosis **(BIII)**. However, a negative result on an initial NAAT followed by a positive result on a subsequent test does not necessarily mean a person has been reinfected; this can occur due to intermittent detection of viral RNA.[14] When the results for an initial and a subsequent test are positive, comparative viral sequence data from both tests are needed to distinguish between the persistent presence of viral fragments and reinfection. In the absence of viral sequence data, the cycle threshold (Ct) value from a positive NAAT result 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 used to guide clinical decisions.

Antigen Testing for SARS-CoV-2 Infection

Antigen-based diagnostic tests (which detect viral antigens) are less sensitive than laboratory-based NAATs, 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. Early data suggest that antigen tests can detect the Omicron variant, but they may have lower sensitivity to this variant compared to earlier variants.[22] Advantages of antigen tests include 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 (e.g., long-term care facilities, schools, dormitories, correctional facilities) and community settings where preventing transmission is critical. These tests can also be used to inform decisions about the use of post-exposure prophylaxis (PEP). Antigen 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. The CDC has developed an antigen testing algorithm for persons in congregate living settings and community settings who have symptoms of COVID-19, those who are asymptomatic and have a close contact with COVID-19, and those who are asymptomatic and have no known exposure to a person with COVID-19.[23] The CDC testing algorithm

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recommends performing additional confirmatory testing with a laboratory-based NAAT when a person who is strongly suspected of having SARS-CoV-2 infection (i.e., a person who is symptomatic) receives a negative result and when a person in a congregate living setting is asymptomatic but receives a positive result. People in congregate living settings who test positive for SARS-CoV-2 infection may need to be isolated as a group; therefore, correct identification of these individuals is especially important in this setting.[23]

Antigen tests can yield false positive results for a variety of reasons, including:

- Incomplete adherence to the instructions for antigen test performance (e.g., 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); *and*
- 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 to occur (i.e., the development of detectable immunoglobulin [Ig] M and/or IgG antibodies to SARS-CoV-2),[24-29] the Panel **does not recommend** using 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 from the FDA.[30] 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, including:

- Important performance characteristics of many of the commercially available serologic tests have not been fully characterized, including the sensitivity and specificity of these tests (i.e., the rates of true positive and true negative results). Only serologic assays that have FDA EUAs should be used in public health or clinical settings. 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 detects neutralizing antibodies from recent or prior SARS-CoV-2 infection. It is unknown whether 1 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.

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Serologic Testing and Immunity to SARS-CoV-2 Infection

The FDA has issued EUAs for more than 80 SARS-CoV-2 serologic tests since the start of the pandemic. However, these tests are not currently authorized for routine use in making individual medical decisions.[30] SARS-CoV-2 serologic tests are authorized for detecting antibodies, but their ability to predict protective immunity has not been validated. The majority of these tests are not standardized. Furthermore, as SARS-CoV-2 is not a well-conserved virus, mutations in the receptor binding domain of the virus could lead to decreased binding affinity between antibodies and SARS-CoV-2-specific antigens.

Given the available information, there is insufficient evidence for the Panel to recommend either for or against the use of SARS-CoV-2 serologic testing to assess for immunity or to guide clinical decisions about using COVID-19 vaccines or anti-SARS-CoV-2 monoclonal antibodies in certain people.

If a serologic test is performed, the result should be interpreted with caution. It remains unclear how long SARS-CoV-2 antibodies persist following either infection or vaccination. A negative serologic test result also does not preclude prior SARS-CoV-2 infection or vaccination against COVID-19. Some people who are infected with SARS-CoV-2 or who are vaccinated against COVID-19 may not develop measurable antibodies (e.g., those who are immunocompromised). It is presumed that those who do not have measurable antibodies after vaccination are at higher risk of SARS-CoV-2 infection.

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

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

- Differentiate between SARS-CoV-2 antibody responses to natural infection and vaccine-induced antibody responses to the SARS-CoV-2 spike protein antigen. Because nucleocapsid protein is not a constituent of the vaccines that are currently approved by the FDA, available through EUAs, or in late-stage clinical trials, serologic tests that detect antibodies by recognizing nucleocapsid proteins can be used to distinguish between antibody responses to natural infection and vaccine-induced antibody responses.
- Determine who may be eligible to donate convalescent plasma
- Define multisystem inflammatory syndrome in children (MIS-C) and multisystem inflammatory syndrome in adults (MIS-A)
- Estimate the proportion of the population that has been 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;
- Determine whether someone may return to the workplace; *or*
- Assess for immunity to SARS-CoV-2 following vaccination in immunocompetent individuals, except in clinical trials.

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Prevention of SARS-CoV-2 Infection

Last Updated: April 29, 2022

Summary Recommendations

• The COVID-19 Treatment Guidelines Panel (the Panel) recommends COVID-19 vaccination as soon as possible for everyone who is eligible according to the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices **(AI)**.
• The Panel recommends using **tixagevimab 300 mg plus cilgavimab 300 mg (Evusheld)** administered as 2 consecutive 3-mL intramuscular injections **(BIII)** as SARS-CoV-2 pre-exposure prophylaxis (PrEP) for adults and adolescents (aged ≥12 years and weighing ≥40 kg) who do not have SARS-CoV-2 infection, who have not been recently exposed to an individual with SARS-CoV-2 infection, **AND** who:
  • Are moderately to severely immunocompromised and may have an inadequate immune response to COVID-19 vaccination; *or*
  • Are not able to be fully vaccinated with any available COVID-19 vaccines due to a history of severe adverse reactions to a COVID-19 vaccine or any of its components.
• The Food and Drug Administration Emergency Use Authorization states that individuals who received tixagevimab 150 mg plus cilgavimab 150 mg should be given a second dose as soon as possible. The specific dose of tixagevimab plus cilgavimab that an individual should receive depends on the amount of time that has passed since the first dose was administered:
  • If the initial dose was administered ≤3 months prior, the second dose should be tixagevimab 150 mg plus cilgavimab 150 mg.
  • If the initial dose was administered >3 months prior, the second dose should be tixagevimab 300 mg plus cilgavimab 300 mg.
• **Tixagevimab plus cilgavimab is not a substitute for COVID-19 vaccination and should not be used in unvaccinated individuals for whom COVID-19 vaccination is recommended.**
• If supplies of tixagevimab plus cilgavimab are limited, priority for use as PrEP should be given to those who are at the highest risk for severe COVID-19.
• The Panel **recommends against** the use of **bamlanivimab plus etesevimab** and **casirivimab plus imdevimab** for post-exposure prophylaxis (PEP), as the Omicron (B.1.1.529) variant and its subvariants, which are not susceptible to these agents, are currently the dominant SARS-CoV-2 variants circulating in the United States **(AIII)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Weak **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 SARS-CoV-2 is thought to occur primarily through exposure to respiratory droplets. Exposure can occur when someone inhales droplets or particles that contain the virus (with the greatest risk of transmission occurring within 6 feet of an infectious source) or touches their mucous membranes with hands that have been contaminated with the virus. Exhaled droplets or particles can also deposit the virus onto exposed mucous membranes.[1]

Less commonly, airborne transmission of small droplets and particles of SARS-CoV-2 to people farther than 6 feet away can occur; 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 (i.e., >15 minutes) to an infectious person who is in an enclosed space with poor ventilation.[1]

The risk of SARS-CoV-2 transmission can be reduced by covering coughs and sneezes and maintaining a distance of at least 6 feet from others. When consistent distancing is not possible, face coverings may 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

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Centers for Disease Control and Prevention (CDC) recommendations for infection control and the appropriate use of personal protective equipment.[3]

Vaccines

Vaccination is the most effective way to prevent SARS-CoV-2 infection. The COVID-19 Treatment Guidelines Panel (the Panel) recommends COVID-19 vaccination as soon as possible for everyone who is eligible according to CDC's Advisory Committee on Immunization Practices **(AI)**. Three vaccines are authorized or approved for use in the United States to prevent COVID-19. For primary and booster vaccinations, the mRNA vaccines (i.e., BNT162b2 [Pfizer-BioNTech] or mRNA-1273 [Moderna]) are preferable to the Ad26.COV2.S (Johnson & Johnson/Janssen) vaccine due to its risk of serious adverse events.[4] A primary series of COVID-19 vaccinations is recommended for everyone aged ≥5 years in the United States. Certain groups of people should receive additional doses at specified intervals after the primary series of vaccinations. The type and dose of vaccine and the timing of these additional doses depend on the recipient's age and underlying medical conditions. CDC regularly updates the clinical considerations for use of the COVID-19 vaccines that are currently approved by the Food and Drug Administration (FDA) or authorized for use in the United States.[5]

Adverse Events

COVID-19 vaccines are safe and effective. Local and systemic adverse events are relatively common with these vaccines. Most of the adverse events that occurred during vaccine trials were mild or moderate in severity (i.e., they did not prevent vaccinated people from engaging in daily activities) and resolved after 1 or 2 days. There have been a few reports of severe allergic reactions following COVID-19 vaccination, including rare reports of patients who experienced anaphylaxis after receiving an mRNA vaccine.[6,7]

Reports have suggested that there is an increased risk of thrombosis with thrombocytopenia syndrome (TTS) in adults who have received the Ad26.COV2.S vaccine[7] and, rarely, the mRNA-1273 vaccine.[8] TTS is a rare but serious condition that causes blood clots in large blood vessels and low platelet levels. Women aged 30 to 49 years should be aware of the increased risk of TTS. The American Society of Hematology and the American Heart Association/American Stroke Association Stroke Council leadership have published considerations that are relevant to the diagnosis and treatment of TTS that occurs in people who receive the Ad26.COV2.S vaccine. These considerations include information on administering a nonheparin anticoagulant and intravenous immunoglobulin to these patients.[9,10] Given the rarity of this syndrome and the unique treatment required, consider consulting a hematologist when treating these patients.

Myocarditis and pericarditis after COVID-19 vaccination are rare, and most of the reported cases were very mild and self-limiting. These conditions have occurred most often in male adolescents, young adults, and people who have received mRNA vaccines.[11]

Guillain-Barré syndrome (GBS) in people who received the Ad26.COV2.S vaccine is rare. GBS is a neurologic disorder that causes muscle weakness and sometimes paralysis. Most people with GBS fully recover, but some have permanent nerve damage. Onset typically occurs about 2 weeks after vaccination. GBS has mostly been reported in men aged ≥50 years.[11]

CDC provides regular updates on selected adverse events of COVID-19 vaccines on its website.

Vaccination in Pregnant or Lactating People

Pregnant and lactating individuals were not included in the initial COVID-19 vaccine trials. However, CDC, the American College of Obstetricians and Gynecologists (ACOG), and the Society for Maternal-

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Fetal Medicine recommend vaccination for pregnant and lactating people based on the accumulated safety and efficacy data on the use of these vaccines in pregnant people, as well as the increased risk of severe disease in pregnant individuals with COVID-19. These organizations also recommend vaccination for people who are trying to become pregnant or who may become pregnant in the future.[12-17] The ACOG publication includes a guide for clinicians on counseling pregnant patients about COVID-19 vaccination.[18]

Pre-Exposure Prophylaxis

Anti-SARS-CoV-2 Monoclonal Antibodies

Vaccination remains the most effective way to prevent SARS-CoV-2 infection and should be considered the first line of prevention. However, some individuals cannot or may not mount an adequate protective response to COVID-19 vaccines. Others may not have been fully vaccinated because they have a history of severe adverse reactions to a COVID-19 vaccine or its components.

Based on the results of PROVENT, a large randomized controlled trial conducted when the major circulating SARS-CoV-2 variants were Alpha (B.1.1.7), Beta (B.1.351), Delta (B.1.617.2), and Epsilon (B.1.429),[19] the FDA issued an Emergency Use Authorization (EUA) for the anti-SARS-CoV-2 monoclonal antibodies (mAbs) tixagevimab plus cilgavimab (Evusheld). The EUA allows these mAbs to be used as pre-exposure prophylaxis (PrEP) for certain individuals who are at high risk of progressing to severe COVID-19 if they become infected with SARS-CoV-2.[20] A modification in the fragment crystallizable (Fc) region gives these anti-SARS-CoV-2 mAbs prolonged half-lives, resulting in potential protection from SARS-CoV-2 infection for up to 6 months, depending on the variant.

The dose used in the PROVENT trial was tixagevimab 150 mg plus cilgavimab 150 mg, which was the dose that was initially authorized by the FDA. However, in vitro data showed that the BA.1 and BA.1.1 subvariants of the Omicron (B.1.1.529) variant have decreased susceptibility to tixagevimab plus cilgavimab.[20-23] Because of these findings, on February 24, 2022, the FDA revised the EUA to authorize tixagevimab 300 mg plus cilgavimab 300 mg as the dose for individuals who are receiving these anti-SARS-CoV-2 mAbs for the first time.[20] For patients who previously received a dose of tixagevimab 150 mg plus cilgavimab 150 mg, the FDA EUA states that a second dose should be given as soon as possible. The specific dose a patient should receive for their second round of tixagevimab plus cilgavimab depends on the amount of time that has passed since the initial dose (see below). The Omicron BA.2 subvariant has been shown to retain near-full susceptibility to tixagevimab plus cilgavimab in vitro, so the dosing recommendations for these mAbs may be further refined in the future.[20,23,24]

When prescribing tixagevimab plus cilgavimab for SARS-CoV-2 PrEP, clinicians should be aware of some important limitations:

- Tixagevimab plus cilgavimab is authorized for use as PrEP in a population that was not well-represented in the PROVENT trial (i.e., a very small proportion of the participants were immunocompromised).
- There are no clinical trial efficacy data on preventing symptomatic COVID-19 with the tixagevimab 300 mg plus cilgavimab 300 mg dose. The new dose is based on pharmacokinetic/pharmacodynamic (PK/PD) modeling that suggests this dose may have in vivo activity against the Omicron BA.1 and BA.1.1 subvariants.[25]
- Substantial uncertainty in the PK/PD model remains. It is possible that even if the tixagevimab 300 mg plus cilgavimab 300 mg dose is active against the Omicron BA.1 and BA.1.1 subvariants, it would provide only a limited duration (≤3 months) of protection. Limited data inform the timing for repeat doses of tixagevimab plus cilgavimab after the initial dose, and repeat doses of tixagevimab 300 mg plus cilgavimab 300 mg are not included in the current EUA.

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- The safety data on using tixagevimab 300 mg plus cilgavimab 300 mg primarily comes from TACKLE, a Phase 3 clinical trial that evaluated the use of tixagevimab plus cilgavimab for the treatment of patients with mild to moderate COVID-19.[25]
- The tixagevimab 150 mg plus cilgavimab 150 mg dose that was initially authorized by the FDA may not be sufficient to prevent cases of COVID-19 caused by the Omicron BA.1 and BA.1.1 subvariants. There are no clinical data and only limited PK/PD data to guide the administration of repeat doses of tixagevimab plus cilgavimab in those who were previously treated with tixagevimab 150 mg plus cilgavimab 150 mg. Simulations based on population PK models suggest that administering an additional dose of tixagevimab 150 mg plus cilgavimab 150 mg ≤3 months after the initial dose will allow a patient to achieve drug concentrations approximating those observed in people who received tixagevimab 300 mg plus cilgavimab 300 mg as their initial dose. For patients who initially received tixagevimab 150 mg plus cilgavimab 150 mg >3 months ago, the simulations suggest that a repeat dose of tixagevimab 300 mg plus cilgavimab 300 mg is necessary.

Recommendations

Factoring in the limitations outlined above:

- The Panel recommends using **tixagevimab 300 mg plus cilgavimab 300 mg** administered as 2 consecutive 3-mL intramuscular (IM) injections **(BIII)** as SARS-CoV-2 PrEP for adults and adolescents (aged ≥12 years and weighing ≥40 kg) who do not have SARS-CoV-2 infection, who have not been recently exposed to an individual with SARS-CoV-2 infection, who have not previously received this regimen, **AND** who:
  - Are moderately to severely immunocompromised and may have an inadequate immune response to COVID-19 vaccination; *or*
  - Are not able to be fully vaccinated with any available COVID-19 vaccines due to a history of severe adverse reactions to a COVID-19 vaccine or any of its components.
- The FDA EUA states that individuals who received tixagevimab 150 mg plus cilgavimab 150 mg should be given a second dose as soon as possible. The specific dose of tixagevimab plus cilgavimab that an individual should receive depends on the amount of time that has passed since the first dose was administered:
  - If the initial dose was administered ≤3 months prior, the second dose should be tixagevimab 150 mg plus cilgavimab 150 mg.
  - If initial dose was administered >3 months prior, the second dose should be tixagevimab 300 mg plus cilgavimab 300 mg.
- **Tixagevimab plus cilgavimab is not a substitute for COVID-19 vaccination and should not be used in unvaccinated individuals for whom COVID-19 vaccination is recommended.**

Individuals who qualify as having moderate to severe immunocompromising conditions under the FDA EUA for tixagevimab plus cilgavimab are those who:

- Are receiving active treatment for solid tumors and hematologic malignancies.
- Received a solid organ transplant and are receiving immunosuppressive therapy.
- Received chimeric antigen receptor T cell therapy or a hematopoietic stem cell transplant (within 2 years of transplantation or receiving immunosuppression therapy).
- Have a moderate or severe primary immunodeficiency (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome).
- Have advanced or untreated HIV infection (defined as people with HIV and CD4 T lymphocyte

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counts <200 cells/mm^3, a history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV).

- Are receiving active treatment with high-dose corticosteroids (i.e., ≥20 mg prednisone or equivalent per day when administered for ≥2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumor-necrosis blockers, or other immunosuppressive or immunomodulatory biologic agents (e.g., B cell-depleting agents).

Additional Considerations

- Because there are no clinical efficacy data available for tixagevimab 300 mg plus cilgavimab 300 mg, and there are uncertainties about the extent and duration of protection against the Omicron BA.1 and BA.1.1 subvariants, high-risk individuals who receive PrEP should continue to use other measures to protect themselves from infection, especially if these subvariants are circulating within their communities.
- The strength of the Panel's recommendation for tixagevimab 300 mg plus cilgavimab 300 mg is based partly on PK/PD modeling for the Omicron BA.1 and BA.1.1 subvariants and partly on the fact that the BA.2 subvariant has been shown to retain near-full susceptibility to tixagevimab plus cilgavimab in vitro.
- If supplies of tixagevimab plus cilgavimab are limited, priority for use as PrEP should be given to those who are at the highest risk for severe COVID-19.
- If a person has received a COVID-19 vaccine, tixagevimab plus cilgavimab should be administered at least 2 weeks after vaccination.

Clinical Trial Data for Tixagevimab Plus Cilgavimab

PROVENT is an ongoing, Phase 3, double-blind, randomized, placebo-controlled trial that evaluated the use of tixagevimab plus cilgavimab for SARS-CoV-2 PrEP.[19,20] The study enrolled adults aged ≥18 years who had not received a COVID-19 vaccine and who were at increased risk of severe SARS-CoV-2 infection (e.g., those aged ≥60 years or those who had a prespecified comorbidity) or who had an increased risk of acquiring SARS-CoV-2 infection due to their occupation or living situation. The study excluded those with a history of confirmed SARS-CoV-2 infection or who had a positive SARS-CoV-2 antibody result at screening.

The analyzed population included participants who received a negative reverse transcription polymerase chain reaction (RT-PCR) result at baseline. Participants received either tixagevimab 150 mg plus cilgavimab 150 mg (administered as 2 consecutive IM injections; n = 3,460) or placebo (administered as 2 IM injections; n = 1,737). The primary endpoint was symptomatic SARS-CoV-2 infection and a positive RT-PCR result during the 183 days of follow-up.

Once COVID-19 vaccines became available, participants could choose to be unblinded and receive the vaccine during the study. Only the primary endpoints that occurred prior to unblinding or vaccine receipt were included in the analysis, resulting in a median follow-up of 83 days. Baseline characteristics were well-balanced between the arms. Prior to unblinding or vaccination, RT-PCR-confirmed symptomatic SARS-CoV-2 infection was reported for 8 participants (0.2%) in the tixagevimab plus cilgavimab arm and 17 participants (1.0%) in the placebo arm, representing a 77% reduction in the incidence of infection in the tixagevimab plus cilgavimab arm (95% CI, 46% to 90%; $P < 0.001$). A post hoc analysis after a median follow-up period of 6 months showed a relative risk reduction of 82.8% (95% CI, 65.8% to 91.4%) for symptomatic infection in the tixagevimab plus cilgavimab arm. Five cases of COVID-19 were considered to be severe or critical, and 2 COVID-19–related deaths were reported. All of these events occurred in participants who received placebo.

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Adverse events were reported for 35.3% of participants in the tixagevimab plus cilgavimab arm and 34.2% of participants in the placebo arm. Serious adverse events were reported in 1% of participants in each arm; 1 participant in the tixagevimab plus cilgavimab arm had an anaphylactic reaction that was resolved with epinephrine therapy. The incidence of adverse events was similar in both study arms; most events were mild (62%) or moderate (32%). Rare, serious cardiac adverse events occurred in 0.7% of participants in the tixagevimab plus cilgavimab arm and in 0.3% of participants in the placebo arm. All participants who experienced a cardiac event had cardiac risk factors or a history of cardiac disease at baseline. There was no clear temporal pattern between these serious cardiac adverse events and administration of the anti-SARS-CoV-2 mAbs.[20]

TACKLE was a Phase 3 trial that evaluated the use of tixagevimab plus cilgavimab for the treatment of nonhospitalized patients with mild to moderate COVID-19. In this study, 452 high-risk adults aged ≥18 years received a single IM dose of tixagevimab 300 mg plus cilgavimab 300 mg and had a follow-up visit within 183 days (the median follow-up period was 84 days). Adverse events were reported for 29% of participants in the tixagevimab plus cilgavimab arm and for 36% of participants in the placebo arm; the majority of events were mild to moderate in severity. Serious cardiac adverse events were reported for 4 participants; 3 had received tixagevimab plus cilgavimab and 1 had received placebo. All events occurred in participants who had cardiac risk factors or a history of cardiovascular disease.[20]

Other Drugs for Pre-Exposure Prophylaxis

- The Panel **recommends against** the use of any oral drugs for SARS-CoV-2 PrEP, except in a clinical trial **(AIII)**.

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. Please check ClinicalTrials.gov for the latest information.

Hydroxychloroquine, given at different doses and durations, has been studied in randomized controlled trials to assess whether it could prevent SARS-CoV-2 infection in those at risk of being exposed to infected individuals, such as health care workers. One study reported no evidence of a benefit of hydroxychloroquine, and it was ultimately halted due to futility before it reached its target enrollment.[26] In another hydroxychloroquine study, which also did not meet its target enrollment and was stopped early, the majority of the potential transmission events were not confirmed by virologic testing.[27] Neither study demonstrated any evidence of a reduction in the rate of acquiring infection. Both studies reported an increased frequency of mild adverse events in the treatment group.

Post-Exposure Prophylaxis

Anti-SARS-CoV-2 Monoclonal Antibodies

- The Panel **recommends against** the use of **bamlanivimab plus etesevimab** and **casirivimab plus imdevimab** for post-exposure prophylaxis (PEP), as the Omicron variant and its subvariants, which are not susceptible to these agents, are currently the dominant SARS-CoV-2 variants circulating in the United States **(AIII)**.

Vaccination remains a highly effective way to prevent SARS-CoV-2 infection. However, despite the widespread availability of COVID-19 vaccines, some individuals are not fully vaccinated or cannot mount an adequate response to the vaccine. Some of these individuals, if infected, are at high risk of progressing to serious COVID-19. Bamlanivimab plus etesevimab and casirivimab plus imdevimab have previously received FDA EUAs for PEP; however, the Omicron variant and its subvariants are currently the dominant SARS-CoV-2 variants circulating in the United States. The Panel **recommends against** the use of these

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anti-SARS-CoV-2 mAbs because the Omicron variant and its subvariants are not susceptible to them **(AIII)**.

Chloroquine and Hydroxychloroquine

- The Panel **recommends against** the use of **hydroxychloroquine** for SARS-CoV-2 PEP **(AI)**.

Both chloroquine and hydroxychloroquine have in vitro activity against SARS-CoV and SARS-CoV-2.[28,29] A small cohort study without a control group suggested that hydroxychloroquine might reduce the risk of SARS-CoV-2 transmission to close contacts.[30] There have been several large trials to determine whether hydroxychloroquine can reduce the risk of infection after exposure to individuals infected with SARS-CoV-2. These studies used different dose schedules and targeted different at-risk populations. In addition, some studies were unable to confirm infection using molecular or antigen tests. None of these studies demonstrated any evidence of efficacy for hydroxychloroquine, and all showed a higher risk of generally mild adverse events in those who received the drug.[31-33]

Other Drugs for Post-Exposure Prophylaxis

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

A number of other agents (e.g., ivermectin, hyperimmune gamma globulin, convalescent plasma, interferons, tenofovir with or without emtricitabine, vitamin D) are currently being investigated for SARS-CoV-2 PEP. The latest clinical trials for SARS-CoV-2 PEP can be found at ClinicalTrials.gov.

High concentrations of ivermectin have been shown to inhibit SARS-CoV-2 replication in vitro.[34,35] Population data indicated that countrywide, mass-use of prophylactic chemotherapy for parasitic infections, including the use of ivermectin, was associated with a lower incidence of COVID-19.[36] At this time, few clinical trials have evaluated the safety and efficacy of using ivermectin for SARS-CoV-2 PrEP or PEP. Although several studies have reported potentially promising results, the findings are limited by the design of the studies, their small sample sizes, and the lack of details regarding the safety and efficacy of ivermectin.

In a descriptive, uncontrolled, interventional study of 33 contacts of patients with laboratory-confirmed SARS-CoV-2 infection, no cases of SARS-CoV-2 infection were identified within 21 days of initiating ivermectin for PEP.[37] In a small case-control study in SARS-CoV-2-exposed health care workers, 186 participants who became infected were matched with 186 uninfected controls. Of those who received ivermectin after exposure to SARS-CoV-2, 38 were in the infected group and 77 were in the uninfected group, which led the investigators to conclude that ivermectin reduced the incidence of SARS-CoV-2 infection.[38]

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Clinical Spectrum of SARS-CoV-2 Infection

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Patients with SARS-CoV-2 infection can experience a range of clinical manifestations, from no symptoms to critical illness. 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 [NAAT] 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 an oxygen saturation (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, a respiratory rate >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 aged ≥65 years; having cardiovascular disease, chronic lung disease, sickle cell disease, diabetes, cancer, obesity, or chronic kidney disease; being pregnant; being a cigarette smoker; being a transplant recipient; and receiving 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 a chest X-ray, ultrasound screening, or, if indicated, a computed tomography scan. 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. Although inflammatory markers such as C-reactive protein (CRP), D-dimer, and ferritin are not routinely measured as part of standard care, results from such measurements 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 pregnant patients and making decisions about 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 increase 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 section of the Guidelines.

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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. The normal values for respiratory rate also vary with age in children; therefore, hypoxemia should be the primary criterion used to define severe COVID-19, 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] Increasing the availability of virologic testing for SARS-CoV-2 and reliable serologic assays for SARS-CoV-2 antibodies will help determine the true prevalence of asymptomatic and presymptomatic infection. See Therapeutic Management of Nonhospitalized Adults 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 Nonhospitalized Adults 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 Nonhospitalized Adults 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, PaO_2/FiO_2 <300 mm Hg, a respiratory rate >30 breaths/min, 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 Hospitalized Adults 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.

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Critical Illness

Critically ill patients may have acute respiratory distress syndrome, septic shock that may represent virus-induced distributive shock, cardiac dysfunction, an exaggerated inflammatory response, 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 Adults With COVID-19.

Infectious Complications in Patients With COVID-19

Some patients with COVID-19 may have additional infections that are noted when they present for care or that develop during the course of treatment. These coinfections may complicate treatment and recovery. Older patients or those with certain comorbidities or immunocompromising conditions may be at higher risk for these infections. The use of immunomodulators such as dexamethasone, interleukin-6 inhibitors (e.g., tocilizumab, sarilumab), or Janus kinase inhibitors (e.g., baricitinib, tofacitinib) to treat COVID-19 may also be a risk factor for infectious complications; however, when these therapies are used appropriately, the benefits outweigh the risks.

Infectious complications in patients with COVID-19 can be categorized as follows:

- *Coinfections at Presentation With COVID-19:* Although most individuals present with only SARS-CoV-2 infection, concomitant viral infections, including influenza and other respiratory viruses, have been reported.[12] Community-acquired bacterial pneumonia has also been reported, but it is uncommon, with a prevalence that ranges from 0% to 6% of people with SARS-CoV-2 infection.[12,13] Antibacterial therapy is generally not recommended unless additional evidence for bacterial pneumonia is present (e.g., leukocytosis, the presence of a focal infiltrate on imaging).
- *Reactivation of Latent Infections:* There are case reports of underlying chronic hepatitis B virus and latent tuberculosis infections reactivating in patients with COVID-19 who receive immunomodulators as treatment,[14-16] although the data are currently limited. Reactivation of herpes simplex virus and varicella zoster virus infections have also been reported.[17] Cases of severe and disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with tocilizumab and corticosteroids.[18,19] Many clinicians would initiate empiric treatment (e.g., treatment with ivermectin) with or without serologic testing in patients who are from areas where *Strongyloides* is endemic (i.e., tropical, subtropical, or warm temperate areas).[20]
- *Nosocomial Infections in Patients With COVID-19:* Hospitalized patients with COVID-19 may acquire common nosocomial infections, such as hospital-acquired pneumonia (including ventilator-associated pneumonia), line-related bacteremia or fungemia, catheter-associated urinary tract infection, and *Clostridioides difficile*-associated diarrhea. Early diagnosis and treatment of these infections are important for improving outcomes in these patients.
- *Opportunistic Fungal Infections:* Invasive fungal infections, including aspergillosis and mucormycosis, have been reported in hospitalized patients with COVID-19.[21-24] Although these infections are relatively rare, they can be fatal, and they may be more commonly seen in immunocompromised patients and in patients who are on mechanical ventilation. The majority of mucormycosis cases have been reported in India and are associated with diabetes mellitus and/or the use of corticosteroids.[25,26] The approach for managing these fungal infections should be the same as the approach for managing invasive fungal infections in other settings.

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SARS-CoV-2 Reinfection

As seen with other viral infections, reinfection with SARS-CoV-2 after recovery from prior infection has been reported.[27] The true prevalence of reinfection is not known, although there are concerns that the frequency of reinfection may increase with the circulation of new variants.[28] SARS-CoV-2 can often be detected from a nasal swab for weeks to months after the initial infection; therefore, repeat testing to evaluate for reinfection should be considered only for those who have recovered from the initial infection and present with COVID-19-compatible symptoms with no obvious alternate etiology **(AIII)**.[29] Diagnostic testing in this setting is summarized in Testing for SARS-CoV-2 Infection. In addition, if reinfection is suspected, guidelines for the diagnosis and evaluation of suspected SARS-CoV-2 reinfection are provided by the Centers for Disease Control and Prevention (CDC).[30]

It has been speculated that reinfection may occur more frequently in those who have a less robust immune response during the initial infection, as is often reported in those with mild illness. Reinfection may also occur as initial immune responses wane over time. Nevertheless, one review noted that SARS-CoV-2 reinfection occurred after previous severe disease in three cases and as early as 3 weeks after the initial infection was diagnosed.[31] A public site that posts a variety of published and unpublished reports of reinfection notes that reinfection has occurred anywhere from a few weeks to many months after the initial infection, and it occasionally follows episodes of severe COVID-19.[32] Although data are limited, there is no evidence to suggest that the treatment of suspected or documented SARS-CoV-2 reinfection should be different from the treatment used during the initial infection, as outlined in Therapeutic Management of Nonhospitalized Adults With COVID-19 and Therapeutic Management of Hospitalized Adults 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. Data about the incidence, natural history, and etiology of these symptoms are emerging. However, these reports have several limitations. For example, there is currently no agreed-upon case definition for persistent symptoms or organ dysfunction after acute COVID-19. In addition, most of these reports only included patients who attended post-COVID-19 clinics, and they often lack comparator groups. No specific treatments for the persistent effects of COVID-19 have yet been identified, although this COVID-19 rapid guideline proposes general management strategies.

The nomenclature for this phenomenon is evolving, and there is no established clinical terminology to date. It has been referred to as post-COVID-19 condition, or, colloquially, "long COVID," and affected patients have been referred to as "long haulers." The term "post-acute sequelae of COVID-19" (PASC) has also been used to describe late sequelae of SARS-CoV-2 infection that include these persistent symptoms, as well as other delayed syndromes such as MIS-C and multisystem inflammatory syndrome in adults (MIS-A). To date, no case definition and no specific time frame have been established to define the syndrome of persistent symptoms and/or organ dysfunction after acute COVID-19. However, CDC recently proposed defining late sequelae as sequelae that extend >4 weeks after initial infection.[33,34] The Patient-Led Research Collaborative for COVID-19 defines long COVID as a collection of symptoms that develop during or following a confirmed or suspected case of COVID-19 and that continue for >28 days.[35] Incidence rates vary widely, from about 10% in some reports to one cohort study in which 87% of patients reported at least one persistent symptom.[36]

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 Introduction to Critical Care Management of Adults With COVID-19 for information on PICS).[37,38]

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Despite the limitations of the available descriptive data on these persistent symptoms, some representative studies have suggested that common findings include fatigue, joint pain, chest pain, palpitations, shortness of breath, cognitive impairment, and worsened quality of life.[39,40]

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; this included 26% of patients aged 18 to 34 years, 32% of those aged 35 to 49 years, and 47% of those aged ≥50 years.[38] 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 returned to baseline health when interviewed at a median of 16 days from the testing date.

In a cohort study from Wuhan, China, 1,733 discharged patients with COVID-19 were evaluated for persistent symptoms at a median of 186 days after symptom onset.[41] The most common symptoms were fatigue or muscle weakness and sleep difficulties (reported among 63% and 26% of participants, respectively). Anxiety or depression was reported among 23% of patients.

In a longitudinal prospective cohort of mostly outpatients with laboratory-confirmed SARS-CoV-2 infection at the University of Washington, 177 participants completed a follow-up questionnaire between 3 and 9 months after illness onset.[42] Overall, 91% of the respondents were outpatients (150 with mild illness and 11 with no symptoms), and only 9% had moderate or severe disease that required hospitalization. Among those who reported symptoms, 33% of outpatients and 31% of hospitalized patients reported at least one persistent symptom. Persistent symptoms were reported by 27% of the patients aged 18 to 39 years, 30% of those aged 40 to 64 years, and 43% of those aged ≥65 years. The most common persistent symptoms were loss of sense of smell or taste and fatigue (both reported by 14% of patients).

Persistent symptoms after acute COVID-19 have also been reported in pregnant people.[43] Systematic data on persistent symptoms in children following recovery from the acute phase of COVID-19 are not currently available, although case reports suggest that children may experience long-term effects similar to those experienced by adults after clinical COVID-19.[44,45] 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 (CFQ11). More than half of patients (67 of 128 patients [52.3%]) reported persistent fatigue at a median of 10 weeks after initial symptoms first appeared. There was no association between illness severity and fatigue.[46] An outpatient service that was developed in Italy for patients recovering from acute COVID-19 reported that 87% of 143 patients surveyed had persistent symptoms for a mean of 60 days after symptom onset. The most common symptom was fatigue, which occurred in 53.1% of these patients.[36]

Cardiopulmonary

A study from the United Kingdom reported that among 100 hospitalized patients with COVID-19 (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.[39] 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%) with COVID-19.[47] In a study

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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.[48] 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%).[49] This assessment of the prevalence of cardiac abnormalities in people with PASC should be viewed with caution, however, as the analysis included only 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.[40,50] Younger patients have been reported to experience more psychiatric symptoms than patients aged >60 years.[39,40] 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.[51-53] One study in the United Kingdom administered cognitive tests to 84,285 participants who had recovered from suspected or confirmed SARS-CoV-2 infection. These participants had worse performances across multiple domains than would be expected for people with the same ages and demographic profiles; this effect was observed even among those who had not been hospitalized.[54] 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 post-acute COVID-19 sequelae and to identify management strategies for patients. More information about ongoing studies can be found at ClinicalTrials.gov.

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Prioritization of Anti-SARS-CoV-2 Therapies for the Treatment and Prevention of COVID-19 When There Are Logistical or Supply Constraints

Last Updated: May 13, 2022

The prioritization guidance in this section should be used **only** when logistical or supply constraints limit the availability of therapies. When there are no supply or logistical constraints, the COVID-19 Treatment Guidelines Panel (the Panel) recommends that therapies for the prevention or treatment of SARS-CoV-2 be prescribed for **any** eligible individual as recommended in these Guidelines.

At times during the pandemic, increased cases of COVID-19 and the emergence of new variants of concern have resulted in logistical or supply constraints that made offering recommended therapies to all eligible patients impossible. In these situations, prioritization of therapy for those who will benefit the most becomes necessary. This section provides guidance on which individuals might receive the greatest benefit from anti-SARS-CoV-2 therapeutics for treatment or prevention when access is limited.

The Panel has recommended several therapeutic agents for the treatment and prevention of SARS-CoV-2 infection in individuals who are at high risk for progression to severe COVID-19. These anti-SARS-CoV-2 therapeutics have the greatest proven clinical benefit for nonhospitalized patients who have risk factors for progression to severe COVID-19. The risks for progression are substantially higher for those who are not vaccinated or who are vaccinated but not expected to mount an adequate immune response to the vaccine.

The Food and Drug Administration provides a broad list of medical conditions or other factors as criteria for use of anti-SARS-CoV-2 agents as treatment or pre-exposure prophylaxis (PrEP).

When it becomes necessary to triage patients for receipt of anti-SARS-CoV-2 therapies or preventive strategies, the Panel suggests prioritizing:

- Treatment of COVID-19 in unvaccinated or incompletely vaccinated individuals with clinical risk factors for severe illness and vaccinated individuals who are not expected to mount an adequate immune response (see Immunocompromising Conditions below)
- Use of tixagevimab plus cilgavimab (Evusheld) as PrEP for individuals who are severely immunocompromised over those who are moderately immunocompromised (see Immunocompromising Conditions below)

Prioritization Strategies When There Are Logistical or Supply Constraints

When logistical or supply constraints limit the availability of anti-SARS-CoV-2 monoclonal antibodies (mAbs) or small-molecule antiviral agents, the Panel recommends that clinicians prioritize their use for patients at highest risk of clinical progression. Providers should use their clinical judgment when prioritizing the use of anti-SARS-CoV-2 mAbs for treatment.

Prioritization schemes should consider how to equitably distribute scarce resources to populations that include individuals who may have less knowledge of or access to these therapies. The availability and distribution of recommended therapies should be monitored to ensure that access to products is equitable.

Patient Prioritization for Treatment

The prioritization table below should be used **only** when logistical or supply constraints limit the availability of therapies. When there are no supply or logistical constraints, the Panel recommends that

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therapies for the prevention or treatment of anti-SARS-CoV-2 be prescribed for **any** eligible individual as recommended in these Guidelines.

The Panel prioritized the following risk groups for anti-SARS-CoV-2 mAbs and antiviral therapy based on 4 key elements: age, vaccination status, immune status, and clinical risk factors. The groups are listed by tier in descending order of priority.

For a list of risk factors, see the Centers for Disease Control and Prevention (CDC) webpage Underlying Medical Conditions Associated With Higher Risk for Severe COVID-19.

Tier	Risk Group
1	• Immunocompromised individuals not expected to mount an adequate immune response to COVID-19 vaccination or SARS-CoV-2 infection due to their underlying conditions, regardless of vaccine status (see Immunocompromising Conditions below); *or* • Unvaccinated individuals at the highest risk of severe disease (anyone aged ≥75 years or anyone aged ≥65 years with additional risk factors).
2	• Unvaccinated individuals not included in Tier 1 who are at risk of severe disease (anyone aged ≥65 years or anyone aged <65 years with clinical risk factors)
3	• Vaccinated individuals at high risk of severe disease (anyone aged ≥75 years or anyone aged ≥65 years with clinical risk factors) **Note:** Vaccinated individuals who have not received a COVID-19 vaccine booster dose are likely at higher risk for severe disease; patients within this tier in this situation should be prioritized for treatment.
4	• Vaccinated individuals at risk of severe disease (anyone aged ≥65 years or anyone aged <65 years with clinical risk factors) **Note:** Vaccinated individuals who have not received a COVID-19 vaccine booster dose are likely at higher risk for severe disease; patients within this tier in this situation should be prioritized for treatment.

Patient Prioritization for Pre-Exposure Prophylaxis

Tixagevimab plus cilgavimab is authorized for use as SARS-CoV-2 PrEP for individuals who have moderate to severe immunocompromising conditions that may result in an inadequate immune response to COVID-19 vaccination. Unlike anti-SARS-CoV-2 agents used for treatment, tixagevimab plus cilgavimab is not authorized for use in unvaccinated individuals unless full vaccination is not possible due to a history of severe allergic reaction to the COVID-19 vaccine. Generally, unless they are also immunocompromised, individuals who qualify for PrEP because of vaccine allergy or contraindication are less likely to suffer severe consequences from SARS-CoV-2 infection than individuals who are moderately to severely immunocompromised.

Immunocompromising Conditions

The CDC website COVID-19 Vaccines for People Who Are Moderately or Severely Immunocompromised provides a list of moderate or severe immunocompromising conditions.[1]

If, because of logistical constraints or supply limitations, anti-SARS-CoV-2 therapies cannot be provided to all individuals who are moderately to severely immunocompromised, the Panel suggests prioritizing their use for patients who are least likely to mount an adequate response to COVID-19 vaccination or SARS-CoV-2 infection and who are at risk for severe outcomes, including (but not limited to) the following populations:

- Patients who are within 1 year of receiving B cell-depleting therapies (e.g., rituximab, ocrelizumab, ofatumumab, alemtuzumab)

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- Patients receiving Bruton's tyrosine kinase inhibitors
- Chimeric antigen receptor T cell recipients
- Post-hematopoietic cell transplant recipients who have chronic graft-versus-host disease or who are taking immunosuppressive medications for another indication
- Patients with hematologic malignancies who are on active therapy
- Lung transplant recipients
- Patients who are within 1 year of receiving a solid organ transplant (other than lung transplant)
- Solid organ transplant recipients who had recent treatment with T cell- or B cell-depleting agents for acute rejection
- Patients with severe combined immunodeficiencies
- Patients with advanced or untreated HIV

If supplies are extremely limited, the Panel suggests prioritizing patients who are more severely immunocompromised and who have additional risk factors for severe disease (as discussed below).

Clinical Risk Factors

Some of the most important risk factors for severe COVID-19 include age (risk increases with each decade after age 50),[2] cancer, cardiovascular disease, chronic kidney disease, chronic lung disease, diabetes, immunocompromising conditions or receipt of immunosuppressive medications, obesity (i.e., body mass index ≥30), and pregnancy. For a complete list of risk factors, including information on the relative risk of severe disease, see the CDC webpage Underlying Medical Conditions Associated With Higher Risk for Severe COVID-19. Of note, the likelihood of developing severe COVID-19 increases when a person has multiple comorbidities.[3]

Although the data on risk factors for severe COVID-19 in children are limited, there is substantial overlap between risk factors in children and those identified in adults. Children aged <1 year or children with obesity, moderate to severe immunosuppression, or complex chronic disease and medical complexity and dependence on respiratory technology are at substantially increased risk of severe disease.[4]

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Clinical Management Summary

Last Updated: April 8, 2022

Two main processes are thought to drive the pathogenesis of COVID-19. Early in the clinical course, the disease is primarily driven by the replication of SARS-CoV-2. Later in the clinical course, the disease appears to be driven by a dysregulated immune/inflammatory response to SARS-CoV-2 that leads to tissue damage. Based on this understanding, it is anticipated that therapies that directly target SARS-CoV-2 would have the greatest effect early in the course of the disease, while immunosuppressive/anti-inflammatory therapies are likely to be more beneficial in the later stages of COVID-19.

The clinical spectrum of SARS-CoV-2 infection includes asymptomatic or presymptomatic infection and mild, moderate, severe, and critical illness. Figure 1 provides guidance for clinicians on the therapeutic management of nonhospitalized adult patients. This includes patients who do not require hospitalization or supplemental oxygen and those who have been discharged from an emergency department or a hospital. Figure 2 provides guidance on the therapeutic management of hospitalized adult patients according to their disease severity and oxygen requirements. Figure 3 provides guidance on the therapeutic management of pediatric patients with multisystem inflammatory syndrome in children (MIS-C).

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Figure 1. Therapeutic Management of Nonhospitalized Adults With COVID-19

PATIENT DISPOSITION	PANEL'S RECOMMENDATIONS
Does Not Require Hospitalization or Supplemental Oxygen	All patients should be offered symptomatic management **(AIII)**. For patients who are at high risk of progressing to severe COVID-19,[a] use 1 of the following treatment options: **Preferred Therapies** *Listed in order of preference:* • **Ritonavir-boosted nirmatrelvir (Paxlovid)[b,c] (AIIa)** • **Remdesivir[c,d] (BIIa)** **Alternative Therapies** *For use ONLY when neither of the preferred therapies are available, feasible to use, or clinically appropriate. Listed in alphabetical order:* • **Bebtelovimab[e] (CIII)** • **Molnupiravir[c,f] (CIIa)** The Panel **recommends against** the use of **dexamethasone[g]** or **other systemic corticosteroids** in the absence of another indication **(AIII)**.
Discharged From Hospital Inpatient Setting in Stable Condition and Does Not Require Supplemental Oxygen	The Panel **recommends against** continuing the use of **remdesivir (AIIa)**, **dexamethasone[g] (AIIa)**, or **baricitinib (AIIa)** after hospital discharge.
Discharged From Hospital Inpatient Setting and Requires Supplemental Oxygen *For those who are stable enough for discharge but who still require oxygen[h]*	There is insufficient evidence to recommend either for or against the continued use of remdesivir or dexamethasone.
Discharged From ED Despite New or Increasing Need for Supplemental Oxygen *When hospital resources are limited, inpatient admission is not possible, and close follow-up is ensured[i]*	The Panel recommends using **dexamethasone** 6 mg PO once daily for the duration of supplemental oxygen (dexamethasone use **should not exceed** 10 days) with careful monitoring for AEs **(BIII)**. Since remdesivir is recommended for patients with similar oxygen needs who are hospitalized,[j] clinicians may consider using it in this setting. As remdesivir requires IV infusions for up to 5 consecutive days, there may be logistical constraints to administering remdesivir in the outpatient setting.

Rating of Recommendations: A = Strong; B = Moderate; C = Weak
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] For a list of risk factors, see the CDC webpage Underlying Medical Conditions Associated With Higher Risk for Severe COVID-19 and the Patient Prioritization for Treatment section in Therapeutic Management of Nonhospitalized Adults With COVID-19.

[b] Ritonavir-boosted nirmatrelvir has significant drug-drug interactions. Clinicians should carefully review a patient's concomitant medications and evaluate potential drug-drug interactions.

[c] If a patient requires hospitalization after starting treatment, the full treatment course can be completed at the health care provider's discretion.

[d] Administration of remdesivir requires 3 consecutive days of IV infusion.

[e] Bebtelovimab is active in vitro against all circulating Omicron subvariants, but there are no clinical efficacy data from placebo-controlled trials that evaluated the use of bebtelovimab in patients who are at high risk of progressing to severe COVID-19. Therefore, bebtelovimab should be used only when the preferred treatment options are not available, feasible to use, or clinically appropriate.

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[f] Molnupiravir has lower efficacy than the preferred treatment options. Therefore, it should be used only when the preferred options are not available, feasible to use, or clinically appropriate.

[g] There is currently a lack of safety and efficacy data on the use of this agent in outpatients with COVID-19; using systemic glucocorticoids in this setting may cause harm.

[h] These individuals should receive oximetry monitoring and close follow-up through telehealth, visiting nurse services, or in-person visits.

[i] Provide an advanced level of home care, including supplemental oxygen (whether patients are receiving oxygen for the first time or are increasing their baseline oxygen requirements), pulse oximetry, laboratory monitoring, and close follow-up through telehealth, visiting nurse services, or in-person visits.

[j] See Therapeutic Management of Hospitalized Adults With COVID-19.

Key: AE = adverse event; CDC = Centers for Disease Control and Prevention; ED = emergency department; IV = intravenous; the Panel = the COVID-19 Treatment Guidelines Panel; PO = orally

Figure 2. Therapeutic Management of Adults Hospitalized for COVID-19 Based on Disease Severity

Disease Severity	Recommendations for Antiviral or Immunomodulator Therapy	Recommendations for Anticoagulation Therapy
Hospitalized but Does Not Require Supplemental Oxygen	The Panel **recommends against** the use of **dexamethasone (AIIa)** or **other corticosteroids (AIII)**.[a] There is insufficient evidence to recommend either for or against the routine use of remdesivir. For patients who are at high risk of disease progression, remdesivir may be appropriate.	For patients without evidence of VTE: • **Prophylactic dose** of heparin, unless contraindicated **(AI)**
Hospitalized and Requires Supplemental Oxygen	Use 1 of the following options: • **Remdesivir**[b,c] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone plus remdesivir**[b,c] **(BIIb)** • **Dexamethasone (BI)** For patients on dexamethasone with rapidly increasing oxygen needs and systemic inflammation, add a second immunomodulatory drug[d] (e.g., **baricitinib**[e] or **tocilizumab**[e]) **(CIIa)**.	For nonpregnant patients with D-dimer levels >ULN who are not at increased bleeding risk:[f] • **Therapeutic dose** of heparin[g] **(CIIa)** For other patients: • **Prophylactic dose** of heparin,[g] unless contraindicated **(AI)**
Hospitalized and Requires Oxygen Through a High-Flow Device or NIV	Use 1 of the following options: • **Dexamethasone (AI)** • **Dexamethasone plus remdesivir**[b] **(BIIb)** For patients with rapidly increasing oxygen needs and systemic inflammation, add either **baricitinib**[e] **(BIIa)** or **IV tocilizumab**[e] **(BIIa)** to 1 of the options above.[d,h]	For patients without evidence of VTE: • **Prophylactic dose** of heparin,[g] unless contraindicated **(AI)**
Hospitalized and Requires MV or ECMO	**Dexamethasone**[i] **(AI)** For patients who are within 24 hours of admission to the ICU: • **Dexamethasone plus IV tocilizumab (BIIa)** If IV tocilizumab is not available or not feasible to use, **IV sarilumab** can be used **(BIIa)**.	For patients without evidence of VTE: • **Prophylactic dose** of heparin,[g] unless contraindicated **(AI)** If patient is started on therapeutic heparin before transfer to the ICU, switch to a **prophylactic dose** of heparin, unless there is a non-COVID-19 indication **(BIII)**.

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

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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[a] Corticosteroids that are prescribed for an underlying condition should be continued.

[b] If the patient progresses to requiring high-flow oxygen, NIV, MV, or ECMO, complete the full course of remdesivir (refer to Table A).

[c] Evidence suggests that the benefit of remdesivir is greatest when the drug is given early in the course of COVID-19 (e.g., within 10 days of symptom onset). Clinical trials have not demonstrated a mortality benefit for remdesivir, but a large, placebo-controlled trial showed that the use of remdesivir reduced time to clinical recovery in hospitalized patients. See Rationale for the Use of Remdesivir below.

[d] Drugs are listed alphabetically. There are no studies that directly compare the use of baricitinib and tocilizumab, and there is insufficient evidence to recommend a drug or class of drug (i.e., JAK inhibitors, anti-IL-6 receptor mAbs) over the other. Treatment decisions should be based on local guidance, drug availability, and patient comorbidities.

[e] If baricitinib and IV tocilizumab are not available or not feasible to use, **tofacitinib** can be used instead of baricitinib **(BIIa)** and **IV sarilumab** can be used instead of IV tocilizumab **(BIIa)**.

[f] Contraindications for the use of therapeutic anticoagulation in patients with COVID-19 include platelet count <50 x 10^9/L, Hgb <8 g/dL, the need for dual antiplatelet therapy, bleeding within the last 30 days that required an ED visit or hospitalization, a history of a bleeding disorder, or an inherited or active acquired bleeding disorder. This list is based on the exclusion criteria from clinical trials; patients with these conditions have an increased risk of bleeding.

[g] Either LMWH or UFH heparin can be used. In general, LMWH is preferred.

[h] The Panel **recommends against** the use of **baricitinib** in combination with **tocilizumab** for the treatment of COVID-19, except in a clinical trial **(AIII)**. Because both baricitinib and tocilizumab are potent immunosuppressants, there is the potential for an additive risk of infection.

[i] The combination of **dexamethasone plus remdesivir** may be considered for patients who have recently been intubated **(CIII)**. The Panel **recommends against** the use of **remdesivir** monotherapy in these patients **(AIIa)**.

Key: ECMO = extracorporeal membrane oxygenation; ED = emergency department; Hgb = hemoglobin; ICU = intensive care unit; IL = interleukin; IV = intravenous; JAK = Janus kinase; LMWH = low-molecular-weight heparin; mAb = monoclonal antibody; MV = mechanical ventilation; NIV = noninvasive ventilation; the Panel = the COVID-19 Treatment Guidelines Panel; UFH = unfractionated heparin; ULN = upper limit of normal; VTE = venous thromboembolism

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Figure 3. Therapeutic Management of Hospitalized Pediatric Patients With MIS-C

PANEL'S RECOMMENDATIONS

MIS-C

Initial treatment for MIS-C includes both immunomodulatory and antithrombotic therapy.

Initial Immunomodulatory Therapy:

- **IVIG** 2 g/kg IBW/dose (up to a maximum total dose of 100 g)[a] IV **plus** low-to-moderate dose **methylprednisolone** (1–2 mg/kg/day) IV[a] or another glucocorticoid at an equivalent dose[a] **(AIIb)**.
- The Panel recommends against the routine use of IVIG monotherapy for the treatment of MIS-C unless glucocorticoid use is contraindicated **(AIIb)**.

Intensification Immunomodulatory Therapy:

- For children with refractory MIS-C who do not improve within 24 hours of initial immunomodulatory therapy, start 1 of the following (listed in alphabetical order) **(AIII)**:
  - High-dose **anakinra** 5–10 mg/kg IV or SUBQ daily **(BIIb)**, *or*
  - **Higher-dose glucocorticoid** (e.g., **methylprednisolone** 10–30 mg/kg/day IV or equivalent glucocorticoid) **(BIIb),**[b] *or*
  - **Infliximab**[c] 5–10 mg/kg IV for 1 dose **(BIIb).**

Antithrombotic Treatment:

- Low-dose **aspirin** (3–5 mg/kg/day, up to maximum daily dose of 81 mg) PO for all patients without risk factors for bleeding **(AIII)**, **AND**
- Anticoagulation for patients who fall under 1 of the following clinical scenarios:
  - **Therapeutic anticoagulation** for patients with large CAAs according to the American Heart Association guidelines for Kawasaki disease **(AIII)**.
  - **Therapeutic anticoagulation** for patients with moderate to severe LV dysfunction who have no risk factors for bleeding **(AIII)**.
  - For patients with MIS-C who do not have large CAAs or moderate to severe LV dysfunction, consider **prophylactic or therapeutic anticoagulation** on an individual basis, taking into consideration risk factors for thrombosis. See below for additional information.

Rating of Recommendations: A = Strong; B = Moderate; C = Weak
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] Duration of therapy may vary. For more information, see Therapeutic Management of Hospitalized Pediatric Patients With Multisystem Inflammatory Syndrome in Children (MIS-C) (With Discussion on Multisystem Inflammatory Syndrome in Adults [MIS-A]).

[b] In certain patients with severe illness, intensification therapy may include dual therapy with higher-dose glucocorticoids and infliximab or anakinra. Anakinra and infliximab **should not be given** in combination.

[c] Infliximab **should not be used** in patients with macrophage activation syndrome.

Key: CAA = coronary artery aneurysm; IBW = ideal body weight; IV = intravenous; IVIG = intravenous immunoglobulin; LV = left ventricular; MIS-C = multisystem inflammatory syndrome in children; PO = oral; SUBQ = subcutaneously

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General Management of Nonhospitalized Patients With Acute COVID-19

Last Updated: December 16, 2021

Summary Recommendations
• Management of nonhospitalized patients with acute COVID-19 should include providing supportive care, considering the use of COVID-19-specific therapy for patients who have a high risk for disease progression, taking steps to reduce the risk of SARS-CoV-2 transmission (including isolating the patient), and advising patients on when to contact a health care provider and seek an in-person evaluation **(AIII)**. • When possible, patients with symptoms of COVID-19 should be triaged via telehealth visits to determine whether they require COVID-19-specific therapy and in-person care **(AIII)**. • Patients with dyspnea should be referred for an in-person evaluation by a health care provider and should be followed closely during the initial days after the onset of dyspnea to assess for worsening respiratory status **(AIII)**. • Management plans should be based on a patient's vital signs, physical exam findings, risk factors for progression to severe illness, and the availability of health care resources **(AIII)**. • See Therapeutic Management of Nonhospitalized Adults With COVID-19 for specific recommendations on using pharmacologic therapy in nonhospitalized patients.
Rating of Recommendations: A = Strong; B = Moderate; C = Weak **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

This section of the Guidelines is intended to provide information to health care providers who are caring for nonhospitalized patients with COVID-19. The COVID-19 Treatment Guidelines Panel's (the Panel) recommendations for pharmacologic management can be found in Therapeutic Management of Nonhospitalized Adults With COVID-19. The Panel recognizes that the distinction between outpatient and inpatient care may be less clear during the COVID-19 pandemic. Patients with COVID-19 may receive care outside traditional ambulatory care or hospital settings if there is a shortage of hospital beds, staff, or resources. Settings such as field hospitals and ambulatory surgical centers and programs such as Acute Hospital Care at Home have been implemented to alleviate hospital bed and staffing shortages.[1] Patients may enter an Acute Hospital Care at Home program from either an emergency department (ED) or an inpatient hospital setting. Health care providers should use their judgment when deciding whether the guidance offered in this section applies to individual patients.

This section focuses on the evaluation and management of:

- Adults with COVID-19 in an ambulatory care setting;
- Adults with COVID-19 following discharge from the ED; *and*
- Adults with COVID-19 following inpatient discharge.

Outpatient evaluation and management in each of these settings may include some or all of the following: telemedicine, remote monitoring, in-person visits, and home visits by nurses or other health care providers.

Managing Patients With COVID-19 in an Ambulatory Care Setting

Approximately 80% of patients with COVID-19 have mild illness that does not warrant medical intervention or hospitalization.[2] Most patients with mild COVID-19 (defined as the absence of viral

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pneumonia and hypoxemia) can be managed in an ambulatory care setting or at home. Patients with moderate COVID-19 (those with viral pneumonia but without hypoxemia) or severe COVID-19 (those with dyspnea, hypoxemia, or lung infiltrates >50%) need in-person evaluation and close monitoring, as pulmonary disease can progress rapidly and require hospitalization.[3]

Health care providers should identify patients who may be at high risk for progression to severe COVID-19; these patients may be candidates for anti-SARS-CoV-2 monoclonal antibody treatment (see Figure 1 in Therapeutic Management of Nonhospitalized Adults with COVID-19). When managing outpatients with COVID-19, clinicians should provide supportive care, take steps to reduce the risk of SARS-CoV-2 transmission (e.g., wear a mask, isolate the patient),[4,5] evaluate the need for COVID-19-specific therapy, and advise patients on when to seek in-person evaluation.[6] Supportive care includes managing symptoms (as described below), ensuring that patients are receiving the proper nutrition, and paying attention to the risks of social isolation, particularly in older adults.[7] Other unique aspects of care for geriatric patients with COVID-19 include considerations related to cognitive impairment, frailty, fall risk, and polypharmacy. Older patients and those with chronic medical conditions have a higher risk for hospitalization and death; however, SARS-CoV-2 infection may cause severe disease and death in patients of any age, even in the absence of any risk factors. The decision to monitor a patient in the outpatient setting should be made on a case-by-case basis.

Assessing the Need for In-Person Evaluation

When possible, patients with symptoms of COVID-19 should be triaged via telehealth visits to determine whether they require COVID-19-specific therapy and in-person care **(AIII)**. Outpatient management may include the use of patient self-assessment tools. During initial triage, clinic staff should determine which patients are eligible to receive supportive care at home and which patients warrant an in-person evaluation.[8] Local emergency medical services, if called by the patient, may also be of help in deciding whether an in-person evaluation is indicated. Patient management plans should be based on the patient's vital signs, physical exam findings, risk factors for progression to severe illness, and the availability of health care resources **(AIII)**.

All patients with dyspnea, oxygen saturation (SpO_2) ≤94% on room air at sea level (if this information is available), or symptoms that suggest higher acuity (e.g., chest pain or tightness, dizziness, confusion or other mental status changes) should be referred for an in-person evaluation by a health care provider **(AIII)**. The criteria used to determine the appropriate clinical setting for an in-person evaluation may vary by location and institution; it may also change over time as new data and treatment options emerge. There should be a low threshold for in-person evaluation of older persons and those with medical conditions that are associated with a risk of progression to severe COVID-19. The individual who performs the initial triage should use their clinical judgement to determine whether a patient requires ambulance transport. There are unique considerations for residents of nursing homes and other long-term care facilities who develop acute COVID-19. Decisions about transferring these patients for an in-person evaluation should be a collaborative effort between the resident (or their health care decision maker), a hospital-based specialist (e.g., an emergency physician or geriatrician), and the clinical manager of the facility.[9]

In some settings where clinical evaluation is challenged by geography, health care provider home visits may be used to evaluate patients.[10] Patients who are homeless should be provided with housing where they can adequately self-isolate. Providers should be aware of the potential adverse effects of prolonged social isolation, including depression and anxiety.[7] All outpatients should receive instructions regarding self-care, isolation, and follow-up, and should be advised to contact a health care provider or a local ED for any worsening symptoms.[11,12] Guidance for implementing home care and isolation of outpatients with COVID-19 is provided by the U.S. Centers for Disease Control and Prevention.

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Clinical Considerations When Managing Patients in an Ambulatory Care Setting

Persons who have symptoms that are compatible with COVID-19 should undergo diagnostic SARS-CoV-2 testing (see Prevention of SARS-CoV-2 Infection). Patients with SARS-CoV-2 infection may be asymptomatic or experience symptoms that are indistinguishable from other acute viral or bacterial infections (e.g., fever, cough, sore throat, malaise, muscle pain, headache, gastrointestinal symptoms). It is important to consider other possible etiologies of symptoms, including other respiratory viral infections (e.g., influenza), community-acquired pneumonia, congestive heart failure, asthma or chronic obstructive pulmonary disease exacerbations, and streptococcal pharyngitis.

In most adult patients, if dyspnea develops, it tends to occur between 4 and 8 days after symptom onset, although it can also occur after 10 days.[13] While mild dyspnea is common, worsening dyspnea and severe chest pain/tightness suggest the development or progression of pulmonary involvement. In studies of patients who developed acute respiratory distress syndrome, progression occurred a median of 2.5 days after the onset of dyspnea.[14-16] Adult outpatients with dyspnea should be followed closely with telehealth or in-person monitoring, particularly during the first few days following the onset of dyspnea, to monitor for worsening respiratory status **(AIII)**.

If an adult patient has access to a pulse oximeter at home, SpO_2 measurements can be used to help assess overall clinical status. Patients should be advised to use pulse oximeters on warm fingers rather than cold fingers for better accuracy. Patients should inform their health care provider if the value is repeatedly below 95% on room air at sea level. Pulse oximetry may not accurately detect occult hypoxemia, especially in Black patients.[3,17,18] Additionally, SpO_2 readings obtained through a mobile phone application may not be accurate enough for clinical use.[19-21] Importantly, oximetry should only be interpreted within the context of a patient's entire clinical presentation (i.e., results should be disregarded if a patient is complaining of increasing dyspnea).

Counseling Regarding the Need for Follow-Up

Health care providers should identify patients who are at high risk for disease progression. These patients may be candidates for anti-SARS-CoV-2 monoclonal antibody treatments, and clinicians should ensure that these patients receive adequate medical follow-up. The frequency and duration of follow-up will depend on the risk for severe disease, the severity of symptoms, and the patient's ability to self-report worsening symptoms. Health care providers should determine whether a patient has access to a phone, computer, or tablet for telehealth; whether they have adequate transportation for clinic visits; and whether they have regular access to food. The clinician should also confirm that the patient has a caregiver who can assist with daily activities if needed.

All patients and/or their family members or caregivers should be counseled about the warning symptoms that should prompt re-evaluation through a telehealth visit or an in-person evaluation in an ambulatory care setting or ED. These symptoms include new onset of dyspnea; worsening dyspnea (particularly if dyspnea occurs while resting or if it interferes with daily activities); dizziness; and mental status changes, such as confusion. Patients should be educated about the time course of these symptoms and the possible respiratory decline that may occur, on average, 1 week after the onset of illness.

Managing Adults With COVID-19 Following Discharge from the Emergency Department

There are no fixed criteria for admitting patients with COVID-19 to the hospital; criteria may vary by region and hospital facilities. Patients with severe disease are typically admitted to the hospital, but some patients with severe disease may not be admitted due to a high prevalence of infection and limited hospital resources. In addition, patients who could receive appropriate care at home but are

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unable to be adequately managed in their usual residential setting are candidates for temporary shelter in supervised facilities, such as a COVID-19 alternative care facility.[22] For example, patients who are living in multigenerational households or who are homeless may not be able to self-isolate and should be provided resources such as dedicated housing units or hotel rooms, when available. Unfortunately, dedicated residential care facilities for COVID-19 patients are not widely available, and community-based solutions for self-care and isolation should be explored.

Treatment with an anti-SARS-CoV-2 monoclonal antibody is recommended for patients with mild to moderate COVID-19 who are not on supplemental oxygen and who have been discharged from the ED but who are at high risk for clinical progression (see Therapeutic Management of Nonhospitalized Adults With COVID-19).

In the cases where institutional resources (e.g., inpatient beds, staff members) are scarce, it may be necessary to discharge an adult patient and provide an advanced level of home care, including supplemental oxygen (if indicated), pulse oximetry, and close follow-up. Although early discharge of those with severe disease is not generally recommended by the Panel, it is recognized that these management strategies are sometimes necessary. In these situations, some institutions are providing frequent telemedicine follow-up visits for these patients or providing a hotline that allows patients to speak with a clinician when necessary. Home resources should be assessed before a patient is discharged from the ED; outpatients should have a caregiver and access to a device that is suitable for telehealth. Patients and/or their family members or caregivers should be counseled about the warning symptoms that should prompt re-evaluation by a health care provider. Special consideration may be given to using certain therapeutics (e.g., dexamethasone) in this setting. For more information, see Therapeutic Management of Nonhospitalized Adults With COVID-19.

Anticoagulants and **antiplatelet therapy** should not be initiated in the ED for the prevention of venous thromboembolism (VTE) or arterial thrombosis if the patient is not being admitted to the hospital, unless the patient has other indications for the therapy or is participating in a clinical trial **(AIII)**. For more information, see Antithrombotic Therapy in Patients With COVID-19. Patients should be encouraged to ambulate, and activity should be increased according to the patient's tolerance.

Managing Adults With COVID-19 Following Hospital Discharge

Most patients who are discharged from the hospital setting should have a follow-up visit with a health care provider soon after discharge. Whether an in-person or a telehealth visit is most appropriate depends on the clinical and social situation. In some cases, adult patients are deemed to be stable for discharge from the inpatient setting even though they still require supplemental oxygen. Special consideration may be given to using certain therapeutics (e.g., dexamethasone) in this setting. For more information, see Therapeutic Management of Nonhospitalized Adults With COVID-19. When possible, these individuals should receive oximetry monitoring and close follow-up through telehealth visits, visiting nurse services, or in-person clinic visits.

Hospitalized patients with COVID-19 should not be routinely discharged while receiving VTE prophylaxis, unless they have another indication or are participating in a clinical trial **(AIII)**. For more information, see Antithrombotic Therapy in Patients With COVID-19. Patients should be encouraged to ambulate, and activity should be increased according to the patient's tolerance.

Considerations in Pregnancy

Managing pregnant outpatients with COVID-19 is similar to managing nonpregnant patients (see Special Considerations in Pregnancy). Clinicians should offer supportive care, take steps to reduce the

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risk of SARS-CoV-2 transmission, and provide guidance on when to seek an in-person evaluation. The American College of Obstetricians and Gynecologists (ACOG) has developed an algorithm to aid the practitioner in evaluating and managing pregnant outpatients with laboratory-confirmed or suspected COVID-19.[23] ACOG has also published recommendations on how to use telehealth for prenatal care and how to modify routine prenatal care when necessary to decrease the risk of SARS-CoV-2 transmission to patients, caregivers, and staff.

In pregnant patients, SpO_2 should be maintained at 95% or above on room air at sea level; therefore, the threshold for monitoring pregnant patients in an inpatient setting may be lower than in nonpregnant patients.[24] In general, there are no changes to fetal monitoring recommendations in the outpatient setting, and fetal management should be similar to the fetal management used for other pregnant patients with medical illness.[25] However, these monitoring strategies can be discussed on a case-by-case basis with an obstetrician. Pregnant and lactating patients should be given the opportunity to participate in clinical trials of outpatients with COVID-19 to help inform decision-making in this population.

Considerations in Children

Children and adolescents with acute COVID-19 are less likely than adults to require medical intervention or hospitalization, and most can be managed in an ambulatory care setting or at home. In general, the need for ED evaluation or hospitalization should be based on the patient's vital signs, physical exam findings (e.g., dyspnea), and risk factors for progression to severe illness. Certain groups, including young infants, children with risk factors, and those with presentations that overlap with multisystem inflammatory syndrome in children (MIS-C), may require hospitalization for more intensive monitoring. However, this should be determined on a case-by-case basis.

Most children with mild or moderate COVID-19, even those with risk factors, will not progress to more severe illness and will recover without specific therapy (see Special Considerations in Children). There is insufficient evidence for the Panel to recommend either for or against the use of anti-SARS-CoV-2 monoclonal antibody products in nonhospitalized children with COVID-19 who have risk factors for severe disease. The available efficacy data for adults suggests that anti-SARS-CoV-2 monoclonal antibody products may be considered for use in children who meet the Food and Drug Administration Emergency Use Authorization (EUA) criteria, especially those who have more than 1 risk factor. The decision to use these products in children should be made on a case-by-case basis in consultation with a pediatric infectious disease specialist. The risk factors that predict progression to severe disease in adults can be used to determine the risk of progression in children aged ≥16 years.

In general, pediatric patients should not continue receiving remdesivir, dexamethasone, or other COVID-19-directed therapies following discharge from an ED or an inpatient setting. Clinicians should refer to Special Considerations in Children for more information on the management of children with COVID-19.

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Therapeutic Management of Nonhospitalized Adults With COVID-19

Last Updated: April 8, 2022

Several therapeutic options are now available for the treatment of nonhospitalized adults with mild to moderate COVID-19 who are at high risk of disease progression. A number of factors affect the selection of the best treatment option for a specific patient. These factors include the clinical efficacy and availability of the treatment option, the feasibility of administering parenteral medications (i.e., remdesivir), the potential for significant drug-drug interactions (e.g., those associated with the use of ritonavir-boosted nirmatrelvir [Paxlovid]), and the regional prevalence of variants of concern (e.g., the regional prevalence of the Omicron BA.2 subvariant may affect which anti-SARS-CoV-2 monoclonal antibodies [mAbs] can be used for treatment).

Figure 1 outlines the COVID-19 Treatment Guidelines Panel's (the Panel) recommendations for using these therapeutic interventions outside the hospital inpatient setting.

Figure 1. Therapeutic Management of Nonhospitalized Adults With COVID-19

PATIENT DISPOSITION	PANEL'S RECOMMENDATIONS
Does Not Require Hospitalization or Supplemental Oxygen	All patients should be offered symptomatic management **(AIII)**. For patients who are at high risk of progressing to severe COVID-19,[a] use 1 of the following treatment options: **Preferred Therapies** *Listed in order of preference:* • **Ritonavir-boosted nirmatrelvir (Paxlovid)[b,c] (AIIa)** • **Remdesivir[c,d] (BIIa)** **Alternative Therapies** *For use ONLY when neither of the preferred therapies are available, feasible to use, or clinically appropriate. Listed in alphabetical order:* • **Bebtelovimab[e] (CIII)** • **Molnupiravir[c,f] (CIIa)** The Panel **recommends against** the use of **dexamethasone[g]** or **other systemic corticosteroids** in the absence of another indication **(AIII)**.
Discharged From Hospital Inpatient Setting in Stable Condition and Does Not Require Supplemental Oxygen	The Panel **recommends against** continuing the use of **remdesivir (AIIa)**, **dexamethasone[g] (AIIa)**, or **baricitinib (AIIa)** after hospital discharge.
Discharged From Hospital Inpatient Setting and Requires Supplemental Oxygen *For those who are stable enough for discharge but who still require oxygen[h]*	There is insufficient evidence to recommend either for or against the continued use of remdesivir or dexamethasone.
Discharged From ED Despite New or Increasing Need for Supplemental Oxygen *When hospital resources are limited, inpatient admission is not possible, and close follow-up is ensured[i]*	The Panel recommends using **dexamethasone** 6 mg PO once daily for the duration of supplemental oxygen (dexamethasone use **should not exceed** 10 days) with careful monitoring for AEs **(BIII)**. Since remdesivir is recommended for patients with similar oxygen needs who are hospitalized,[j] clinicians may consider using it in this setting. As remdesivir requires IV infusions for up to 5 consecutive days, there may be logistical constraints to administering remdesivir in the outpatient setting.

Rating of Recommendations: A = Strong; B = Moderate; C = Weak
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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[a] For a list of risk factors, see the CDC webpage Underlying Medical Conditions Associated With Higher Risk for Severe COVID-19 and the Patient Prioritization for Treatment section below.

[b] Ritonavir-boosted nirmatrelvir has significant drug-drug interactions. Clinicians should carefully review a patient's concomitant medications and evaluate potential drug-drug interactions.

[c] If a patient requires hospitalization after starting treatment, the full treatment course can be completed at the health care provider's discretion.

[d] Administration of remdesivir requires 3 consecutive days of IV infusion.

[e] Bebtelovimab is active in vitro against all circulating Omicron subvariants, but there are no clinical efficacy data from placebo-controlled trials that evaluated the use of bebtelovimab in patients who are at high risk of progressing to severe COVID-19. Therefore, bebtelovimab should be used only when the preferred treatment options are not available, feasible to use, or clinically appropriate.

[f] Molnupiravir has lower efficacy than the preferred treatment options. Therefore, it should be used only when the preferred options are not available, feasible to use, or clinically appropriate.

[g] There is currently a lack of safety and efficacy data on the use of this agent in outpatients with COVID-19; using systemic glucocorticoids in this setting may cause harm.

[h] These individuals should receive oximetry monitoring and close follow-up through telehealth, visiting nurse services, or in-person visits.

[i] Provide an advanced level of home care, including supplemental oxygen (whether patients are receiving oxygen for the first time or are increasing their baseline oxygen requirements), pulse oximetry, laboratory monitoring, and close follow-up through telehealth, visiting nurse services, or in-person visits.

[j] See Therapeutic Management of Hospitalized Adults With COVID-19.

Key: AE = adverse event; CDC = Centers for Disease Control and Prevention; ED = emergency department; IV = intravenous; the Panel = the COVID-19 Treatment Guidelines Panel; PO = orally

Patient Prioritization for Treatment

During surges in cases of SARS-CoV-2 infection, logistical or supply constraints may make it impossible to offer available therapeutics to all the nonhospitalized patients who are eligible to receive them. In these situations, the Panel recommends prioritizing the treatment of patients who are at the highest risk of clinical progression (see Prioritization of Anti-SARS-CoV-2 Therapies for the Treatment and Prevention of COVID-19 When There Are Logistical or Supply Constraints).

In Table A, the Panel has prioritized the risk groups for anti-SARS-CoV-2 therapy based on 4 key elements: age, vaccination status, immune status, and the presence of risk factors for clinical progression. The groups are listed in descending order of priority. For a list of risk factors, see the Centers for Disease Control and Prevention (CDC) website Underlying Medical Conditions Associated With Higher Risk for Severe COVID-19.

Table A. Patient Risk Groups for Prioritizing the Use of Anti-SARS-CoV-2 Therapy

Tier	Risk Groups
1	• Immunocompromised individuals who are not expected to mount an adequate immune response to COVID-19 vaccination or SARS-CoV-2 infection due to their underlying conditions, regardless of their vaccine status (see Immunocompromising Conditions below); *or* • Unvaccinated individuals who are at the highest risk of severe disease (anyone aged ≥75 years or anyone aged ≥65 years with additional risk factors)
2	• Unvaccinated individuals who are at risk of severe disease and who are not included in Tier 1 (anyone aged ≥65 years or anyone aged <65 years with clinical risk factors)

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Tier	Risk Groups
3	• Vaccinated individuals who are at high risk of severe disease (anyone aged ≥75 years or anyone aged ≥65 years with clinical risk factors) • Vaccinated individuals who have not received a COVID-19 vaccine booster dose are likely to be at higher risk for severe disease; patients who have not received a booster dose and who are within this tier should be prioritized for treatment.
4	• Vaccinated individuals who are at risk of severe disease (anyone aged ≥65 years or anyone aged <65 with clinical risk factors) • Vaccinated individuals who have not received a COVID-19 vaccine booster dose are likely to be at higher risk for severe disease; patients who have not received a booster dose and who are within this tier should be prioritized for treatment.

Immunocompromising Conditions

The CDC website COVID-19 Vaccines for Moderately or Severely Immunocompromised People provides a list of moderate and severe immunocompromising conditions.

If these anti-SARS-CoV-2 agents cannot be provided to all moderately to severely immunocompromised individuals because of logistical constraints or supply limitations, the Panel suggests prioritizing their use for those who are least likely to mount an adequate response to COVID-19 vaccination or SARS-CoV-2 infection and who are at risk for severe outcomes. This includes:

- Patients who are within 1 year of receiving B cell-depleting therapies (e.g., rituximab, ocrelizumab, ofatumumab, alemtuzumab)
- Patients who are receiving Bruton's tyrosine kinase inhibitors
- Chimeric antigen receptor T cell recipients
- Post-hematopoietic cell transplant recipients who have chronic graft versus host disease or who are taking immunosuppressive medications for another indication
- Patients with hematologic malignancies who are on active therapy
- Lung transplant recipients
- Patients who are within 1 year of receiving a solid organ transplant (other than a lung transplant)
- Solid organ transplant recipients with recent treatment for acute rejection with T cell- or B cell-depleting agents
- Patients with severe combined immunodeficiencies
- Patients with untreated HIV who have CD4 T lymphocyte cell counts <50 cells/mm^3

If supplies are extremely limited, the Panel suggests prioritizing those who are more severely immunocompromised (based on the list above) and who have additional risk factors for severe disease.

Table B. Dosing Regimens for the Drugs Recommended for High-Risk, Nonhospitalized Adults With Mild to Moderate COVID-19, Listed in Order of Preference Based on Efficacy and Convenience of Use

Drug Name	Dosing Regimen	Time From Symptom Onset[a]
Ritonavir-Boosted Nirmatrelvir (Paxlovid)	**eGFR ≥60 mL/min:** • Nirmatrelvir 300 mg with RTV 100 mg PO twice daily for 5 days **eGFR ≥30 to <60 mL/min:** • Nirmatrelvir 150 mg with RTV 100 mg PO twice daily for 5 days	≤5 days

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Drug Name	Dosing Regimen	Time From Symptom Onset[a]
Ritonavir-Boosted Nirmatrelvir (Paxlovid), continued	**eGFR <30 mL/min:** **• Not recommended** **Severe Hepatic Impairment (Child-Pugh Class C):** **• Not recommended**	≤5 days
Remdesivir	RDV 200 mg IV on Day 1, followed by RDV 100 mg IV once daily on Days 2 and 3.[b,c] Each infusion should be administered over 30–120 minutes. Patients should be observed for ≥1 hour after infusion as clinically appropriate.	≤7 days
Bebtelovimab	BEB 175 mg as a single IV injection, administered over ≥30 seconds. Patients should be observed for ≥1 hour after injection.	≤7 days
Molnupiravir	Molnupiravir 800 mg PO twice daily for 5 days	≤5 days

[a] Per EUA criteria or clinical trial entry criteria.

[b] An eGFR <30 mL/min at screening or <90 days before screening was considered an exclusion criterion in the outpatient RDV study PINETREE, but only if a participant's weight was <48 kg. See the Remdesivir section for a discussion of RDV use in patients with renal impairment.

[c] If RDV is administered to patients who have a new or increasing need for supplemental oxygen but who are discharged from the ED because hospital resources are limited and inpatient admission is not possible, the total duration of therapy is ≤5 days.

Key: BEB = bebtelovimab; ED = emergency department; eGFR = estimated glomerular filtration rate; EUA = Emergency Use Authorization; IV = intravenous; PO = orally; RDV = remdesivir; RTV = ritonavir

Symptom Management

Symptomatic treatment includes using over-the-counter antipyretics, analgesics, or antitussives for fever, headache, myalgias, and cough. Patients with dyspnea may benefit from resting in the prone position rather than the supine position.[1] Health care providers should consider educating patients about breathing exercises, as severe breathlessness may cause anxiety.[2] Patients should be advised to drink fluids regularly to avoid dehydration. Rest is recommended as needed during the acute phase of COVID-19, and ambulation and other forms of activity should be increased according to the patient's tolerance. Patients should be educated about the variability in time to symptom resolution and complete recovery.

Rationale for the Use of Specific Agents Listed in Figure 1

The Panel's recommendations for the therapeutics that are used to treat nonhospitalized patients with mild to moderate COVID-19 who are at risk of clinical progression are based on the results of clinical trials for the antiviral drugs (ritonavir-boosted nirmatrelvir, remdesivir, and molnupiravir) and on laboratory assessments of the activity of the anti-SARS-CoV-2 mAb bebtelovimab.

A number of factors affect the selection of the best treatment option for a specific patient. These factors include the clinical efficacy of the treatment option against circulating variants, the availability of the treatment option, the feasibility of administering parenteral medications (i.e., remdesivir, bebtelovimab), and the potential for significant drug-drug interactions (i.e., the interactions associated with using ritonavir-boosted nirmatrelvir).

The Panel recommends ritonavir-boosted nirmatrelvir and remdesivir as preferred therapy options because Phase 3 randomized placebo-controlled trials have reported high clinical efficacies for these agents in patients with COVID-19.[3,4] The Panel favors the use of ritonavir-boosted nirmatrelvir in most high-risk, nonhospitalized patients with mild to moderate COVID-19. If ritonavir-boosted nirmatrelvir is

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not available or cannot be used because of drug interactions, the Panel recommends using remdesivir as the second option.

The Panel recommends bebtelovimab and molnupiravir as alternative therapy options. These drugs should **ONLY** be used when neither of the preferred treatment options are available, feasible to use, or clinically appropriate. The Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for bebtelovimab based on in vitro data that showed that bebtelovimab has activity against all circulating Omicron subvariants and clinical efficacy data from a small, Phase 2 clinical trial in individuals with mild to moderate COVID-19 who were at low risk of disease progression.[5] However, there are no Phase 3 clinical trial data for bebtelovimab. Molnupiravir had lower clinical efficacy in Phase 3 clinical trials than the preferred treatment options.

The Panel previously recommended the anti-SARS-CoV-2 mAb sotrovimab as a treatment option for certain nonhospitalized patients with COVID-19. However, sotrovimab, which is active against the Omicron BA.1 and BA.1.1 subvariants, has substantially decreased in vitro activity against the Omicron BA.2 subvariant that has become the dominant subvariant in the United States.[6-8] Because the Omicron BA.2 subvariant is now the dominant circulating subvariant in all regions of the United States, the distribution of sotrovimab has been paused, and the Panel no longer recommends using sotrovimab to treat COVID-19.

There are currently no clinical trial data that directly compare the clinical efficacies of these 4 therapies, and there are no data on the use of combinations of antiviral agents and/or anti-SARS-CoV-2 mAbs for the treatment of COVID-19. The rationale for each of the Panel's recommendations is discussed below.

Ritonavir-Boosted Nirmatrelvir (Paxlovid)

Nirmatrelvir is an orally bioavailable protease inhibitor that is active against M^{PRO}, a viral protease that plays an essential role in viral replication by cleaving the 2 viral polyproteins.[9] It has demonstrated antiviral activity against all coronaviruses that are known to infect humans.[10] Nirmatrelvir is packaged with ritonavir (as Paxlovid), a strong cytochrome P450 (CYP) 3A4 inhibitor and pharmacokinetic boosting agent. Ritonavir is required to increase nirmatrelvir concentrations to the target therapeutic ranges.

Recommendations

- The Panel recommends using **nirmatrelvir 300 mg with ritonavir 100 mg (Paxlovid)** orally (PO) twice daily for 5 days in those aged ≥12 years and weighing ≥40 kg; treatment should be initiated as soon as possible and within 5 days of symptom onset **(AIIa)**.
- Ritonavir-boosted nirmatrelvir has significant and complex drug-drug interactions, primarily due to the ritonavir component of the combination.
- Before prescribing ritonavir-boosted nirmatrelvir, clinicians **should carefully review the patient's concomitant medications**, including over-the-counter medications and herbal supplements, to evaluate potential drug-drug interactions.
- The EUA fact sheet for ritonavir-boosted nirmatrelvir, the Liverpool COVID-19 Drug Interactions website, and guidance from the Ontario COVID-19 Science Advisory Table should be utilized to identify and manage drug-drug interactions. A quick reference guide is also provided in the Ritonavir-Boosted Nirmatrelvir (Paxlovid) section.

In the EPIC-HR trial, ritonavir-boosted nirmatrelvir reduced the risk of hospitalization or death by 88% compared to placebo in nonhospitalized adults with laboratory-confirmed SARS-CoV-2 infection.[3,11] This efficacy is comparable to the efficacies reported in similar patient populations for sotrovimab (85% relative reduction)[12] and remdesivir (87% relative reduction)[4] and greater than the efficacy reported for molnupiravir in this setting (30% relative reduction).[13]

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Ritonavir-boosted nirmatrelvir is expected to be active against all Omicron subvariants, although clinical efficacy data are lacking.[14-16] Because ritonavir-boosted nirmatrelvir has the potential for significant drug-drug interactions with concomitant medications, this regimen may not be a safe choice for all patients (see Ritonavir-Boosted Nirmatrelvir [Paxlovid]). However, because ritonavir-boosted nirmatrelvir is the only highly effective oral antiviral available for the treatment of COVID-19, drug interactions that can be safely managed should not preclude the use of this medication.

The EPIC-HR trial excluded pregnant and lactating individuals. Ritonavir has been used extensively during pregnancy in people with HIV, which suggests that it has an acceptable safety profile during pregnancy. Based on the mechanisms of action for both nirmatrelvir and ritonavir and the available animal data, the Panel recommends ritonavir-boosted nirmatrelvir for pregnant patients because the potential benefits likely outweigh the risks.

Remdesivir

Remdesivir is currently approved by the FDA for use in hospitalized patients with COVID-19 and in nonhospitalized patients with mild to moderate COVID-19 who are at high risk of disease progression. Remdesivir has been studied in nonhospitalized patients with mild to moderate COVID-19 who were at high risk of progressing to severe disease. The PINETREE trial showed that 3 consecutive days of intravenous (IV) remdesivir resulted in an 87% relative reduction in the risk of hospitalization or death compared to placebo.[4] Remdesivir is expected to be active against the Omicron variant, although in vitro and in vivo data are currently limited.[16] See the Remdesivir section for more details.

Recommendations

- The Panel recommends using **remdesivir 200 mg** IV on Day 1, followed by **remdesivir 100 mg** IV once daily on Days 2 and 3 in those aged ≥12 years and weighing ≥40 kg; treatment should be initiated as soon as possible and within 7 days of symptom onset **(BIIa)**.
- Remdesivir should be administered in a setting where severe hypersensitivity reactions, such as anaphylaxis, can be managed. Patients should be monitored during the infusion and observed for at least 1 hour after infusion as clinically appropriate.

Because remdesivir requires IV infusions for 3 consecutive days, there may be logistical constraints to administering remdesivir in many settings. However, it is an option if ritonavir-boosted nirmatrelvir is not available.

The Panel recommends using remdesivir, dexamethasone, or both drugs together in hospitalized patients who require supplemental oxygen (see Therapeutic Management of Hospitalized Adults With COVID-19). When remdesivir is used in this setting, it is administered as a once-daily IV infusion for 5 days. There are rare instances when hospital resources are limited and admission to an inpatient unit is not possible for patients who need to initiate supplemental oxygen in the emergency department (ED) or who have increasing supplemental oxygen requirements. In these cases, patients may be discharged from the ED with close monitoring and are often prescribed dexamethasone for up to 10 days. Since remdesivir is often recommended for hospitalized patients with COVID-19 who have similar oxygen needs, clinicians can consider using it in this setting. However, it should be noted that the data on using remdesivir in this situation are limited, and administering IV infusions for up to 5 consecutive days can be difficult in the outpatient setting.

Bebtelovimab

Bebtelovimab is a recombinant neutralizing human mAb that binds to the spike protein of SARS-CoV-2. In vitro data suggest that bebtelovimab has activity against a broad range of SARS-CoV-2 variants, including the Omicron variant and its BA.1, BA.1.1, and BA.2 subvariants.[7,17] However, to date, the

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clinical trial data for bebtelovimab come from a single Phase 2 randomized placebo-controlled trial in patients with COVID-19 who were at low risk of progressing to severe disease. The trial showed no unexpected safety events, and patients who received bebtelovimab had more rapid viral decay than those who received the placebo.

Recommendations

- The Panel recommends using **bebtelovimab 175 mg** IV in those aged ≥12 years **ONLY** when ritonavir-boosted nirmatrelvir (Paxlovid) and remdesivir are not available, feasible to use, or clinically appropriate; treatment should be initiated as soon as possible and within 7 days of symptom onset **(CIII)**.
- Bebtelovimab should be administered in a setting where severe hypersensitivity reactions, such as anaphylaxis, can be managed. Patients should be monitored during the infusion and observed for at least 1 hour after infusion.

Although there are insufficient data on hospitalization and mortality outcomes for patients with COVID-19 who were at high risk of disease progression and who received bebtelovimab, this agent has a mechanism of action that is similar to other anti-SARS-CoV-2 mAbs that have been shown to reduce rates of hospitalization or death among high-risk patients in Phase 3 trials. Therefore, the in vitro data and Phase 2 clinical trial data for bebtelovimab, coupled with the clinical efficacy data for other anti-SARS-CoV-2 mAbs, support the use of bebtelovimab in high-risk patients with COVID-19 when preferred treatment options are not available, feasible to use, or clinically appropriate.

Molnupiravir

Molnupiravir is the oral prodrug of beta-D-N4-hydroxycytidine (NHC), a ribonucleoside that has broad antiviral activity against RNA viruses. NHC uptake by viral RNA-dependent RNA-polymerases results in viral mutations and lethal mutagenesis.[18,19]

Molnupiravir has potent antiviral activity against SARS-CoV-2.[19] As a mutagenic ribonucleoside antiviral agent, there is a theoretical risk that molnupiravir will be metabolized by the human host cell and incorporated into the host DNA, leading to mutations. Molnupiravir has been evaluated in 2 in vivo rodent mutagenicity assays. One study produced equivocal results; in the other study, there was no evidence for mutagenicity. The FDA concluded that, based on the available genotoxicity data and the 5-day duration of treatment, molnupiravir has a low risk for genotoxicity.[20] In addition, there have been concerns about the potential effects of molnupiravir on SARS-CoV-2 mutation rates; the FDA is requiring the manufacturer to establish a process to monitor genomic databases for the emergence of SARS-CoV-2 variants.

Molnupiravir is expected to be active against the Omicron variant, although in vitro and in vivo data are currently limited.[16]

Recommendation

- The Panel recommends using **molnupiravir 800 mg** PO twice daily for 5 days in those aged ≥18 years **ONLY** when ritonavir-boosted nirmatrelvir (Paxlovid) and remdesivir are not available, feasible to use, or clinically appropriate **(CIIa)**.

In the MOVe-OUT trial, molnupiravir reduced the rate of hospitalization or death by 30% compared to placebo in nonhospitalized patients with COVID-19.[13,20] Even though the different treatment options have not been directly compared in clinical trials, the Panel recommends using molnupiravir only when ritonavir-boosted nirmatrelvir and remdesivir are not available or cannot be used, because molnupiravir has lower efficacy than the other options.

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The FDA EUA states that molnupiravir is not recommended for use in pregnant patients due to concerns about the instances of fetal toxicity observed during animal studies. However, when other therapies are not available, pregnant people with COVID-19 who are at high risk of progressing to severe disease may reasonably choose molnupiravir therapy after being fully informed of the risks, particularly if they are beyond the time of embryogenesis (i.e., >10 weeks' gestation). The prescribing clinician should document that a discussion of the risks and benefits occurred and that the patient chose this therapy.

People who engage in sexual activity that may result in conception should use effective contraception during and following treatment with molnupiravir.

Dexamethasone

The Panel **recommends against** the use of **dexamethasone** or **other systemic glucocorticoids** to treat outpatients with mild to moderate COVID-19 who do not require hospitalization or supplemental oxygen **(AIII)**. There is currently a lack of safety and efficacy data on the use of these agents, and systemic glucocorticoids may cause harm in these patients. Patients who are receiving **dexamethasone** or **another corticosteroid** for other indications should continue therapy for their underlying conditions as directed by their health care providers **(AIII)**.

In the RECOVERY trial, dexamethasone was shown to reduce mortality in hospitalized patients with COVID-19 who required supplemental oxygen.[21] Nonhospitalized patients who did not require supplemental oxygen were not included in this trial. The Panel **recommends against** the use of **dexamethasone** or **other systemic glucocorticoids** in this population, as there are no clinical trial data to support their use **(AIII)**.

Dexamethasone was stopped at the time of hospital discharge during the RECOVERY trial. For hospitalized patients with COVID-19 who do not require supplemental oxygen after discharge, the Panel **recommends against** the continuation of **dexamethasone (AIIa)**.

In some cases, adult patients are deemed to be stable enough to be discharged from the inpatient setting even though they still require supplemental oxygen. This practice was likely uncommon during the RECOVERY trial; therefore, there is insufficient evidence to recommend either for or against the continued use of dexamethasone after hospital discharge in patients who require supplemental oxygen. The use of corticosteroids can lead to adverse events (e.g., hyperglycemia, neuropsychiatric symptoms, secondary infections), which may be difficult to detect and monitor in an outpatient setting. If a patient continues to receive corticosteroids after discharge, consider continuing corticosteroids for the duration of supplemental oxygen. However, the total duration of corticosteroid use **should not exceed** 10 days (including days during hospitalization). Only patients who showed good tolerance to this therapy prior to discharge should continue to receive corticosteroids after discharge, and these patients should receive oximetry monitoring and close follow-up through telehealth, visiting nurse services, or in-person visits.

In rare cases, patients with COVID-19 who require supplemental oxygen and hospital admission may need to be discharged from the ED due to scarce resources (e.g., in cases where hospital beds or staff are not available). For these patients, the Panel recommends using **dexamethasone** 6 mg PO once daily for the duration of supplemental oxygen (dexamethasone use should not exceed 10 days) with careful monitoring for adverse events **(BIII)**. These patients should receive oximetry monitoring and close follow-up through telehealth, visiting nurse services, or in-person visits.

Other Agents That Have Been Studied or Are Under Investigation for Use in Outpatients With COVID-19

- The Panel **recommends against** the use of **chloroquine** or **hydroxychloroquine** with or without **azithromycin (AI)**, **lopinavir/ritonavir**, and **other HIV protease inhibitors (AIII)** for the

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outpatient treatment of COVID-19.

- The Panel **recommends against** the use of **antibacterial therapy** (e.g., **azithromycin**, **doxycycline**) for the outpatient treatment of COVID-19 in the absence of another indication **(AIII)**.
- Other agents have undergone or are currently undergoing investigation in the outpatient setting. For more information, please refer to the sections of the Guidelines that address:
  - Antiviral agents, such as ivermectin and nitazoxanide
  - Convalescent plasma
  - Immunomodulators, such as colchicine, fluvoxamine, and inhaled corticosteroids
  - Supplements, such as vitamin C, vitamin D, and zinc
- The Panel **recommends against** the use of **anticoagulants** and **antiplatelet therapy** for the prevention of venous thromboembolism or arterial thrombosis unless the patient has other indications for the therapy or is participating in a clinical trial **(AIIa)**. For more information, see Antithrombotic Therapy in Patients With COVID-19.
- Health care providers should provide information about ongoing clinical trials of investigational therapies to eligible outpatients with COVID-19 so they can make informed decisions about participation **(AIII)**.

Concomitant Medication Management

In general, a patient's usual medication and/or supplement regimen should be continued after the diagnosis of COVID-19 (see Considerations for Using Concomitant Medications in Patients With COVID-19). **Angiotensin-converting enzyme inhibitors, statin therapy, nonsteroidal anti-inflammatory drugs,** and **oral, inhaled,** and **intranasal corticosteroids** that are prescribed for comorbid conditions should be continued as directed **(AIII)**. Patients should be advised to avoid the use of nebulized medications in the presence of others to avoid potential aerosolization of SARS-CoV-2.[22] In patients with HIV, antiretroviral therapy should not be switched or adjusted for the purpose of preventing or treating SARS-CoV-2 infection **(AIII)**. For more information, see Special Considerations in People With HIV.

When a patient is receiving an immunomodulating medication, the prescribing clinician should be consulted about the risks and benefits that are associated with a temporary dose reduction or discontinuation. These risks and benefits will depend on the medication's indication and the severity of the underlying condition.

Patients who use a continuous positive airway pressure (CPAP) device or a bilevel positive airway pressure (BiPAP) device to manage obstructive sleep apnea may continue to use their machine. As with nebulizers, patients should be advised to use the device only when they are isolated from others.

Use of Concomitant Medications With Ritonavir-Boosted Nirmatrelvir (Paxlovid)

Ritonavir-boosted nirmatrelvir is one of the preferred agents for the treatment of mild to moderate COVID-19 in nonhospitalized patients who are at risk of clinical progression. It has the potential for significant and complex drug-drug interactions with concomitant medications, primarily due to the ritonavir component of the combination. Boosting with ritonavir, a strong CYP3A inhibitor, is required to increase the exposure of nirmatrelvir to a concentration that is effective against SARS-CoV-2. However, ritonavir may also increase concentrations of certain concomitant medications, thereby increasing the potential for serious and sometimes life-threatening drug toxicities. Additionally,

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ritonavir is an inhibitor, inducer, and substrate of various other drug-metabolizing enzymes and/or drug transporters.

Before prescribing ritonavir-boosted nirmatrelvir, clinicians **should carefully review the patient's concomitant medications**, including over-the-counter medicines, herbal supplements, and recreational drugs. Clinicians should refer to resources such as the Liverpool COVID-19 Drug Interactions website, the Ritonavir-Boosted Nirmatrelvir (Paxlovid) section, and the EUA fact sheet for ritonavir-boosted nirmatrelvir for guidance regarding potential drug-drug interactions.

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Therapeutic Management of Hospitalized Adults With COVID-19

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Figure 2. Therapeutic Management of Adults Hospitalized for COVID-19 Based on Disease Severity

Dosing regimens for the drugs recommended in this figure are listed in Table A below.

Figure 2. Therapeutic Management of Adults Hospitalized for COVID-19 Based on Disease Severity

Disease Severity	Recommendations for Antiviral or Immunomodulator Therapy	Recommendations for Anticoagulation Therapy
Hospitalized but Does Not Require Supplemental Oxygen	The Panel **recommends against** the use of **dexamethasone (AIIa)** or **other corticosteroids (AIII)**.[a] There is insufficient evidence to recommend either for or against the routine use of remdesivir. For patients who are at high risk of disease progression, remdesivir may be appropriate.	For patients without evidence of VTE: • **Prophylactic dose** of heparin, unless contraindicated **(AI)**
Hospitalized and Requires Supplemental Oxygen	Use 1 of the following options: • **Remdesivir**[b,c] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone plus remdesivir**[b,c] **(BIIb)** • **Dexamethasone (BI)** For patients on dexamethasone with rapidly increasing oxygen needs and systemic inflammation, add a second immunomodulatory drug[d] (e.g., **baricitinib**[e] or **tocilizumab**[e]) **(CIIa)**.	For nonpregnant patients with D-dimer levels >ULN who are not at increased bleeding risk:[f] • **Therapeutic dose** of heparin[g] **(CIIa)** For other patients: • **Prophylactic dose** of heparin,[g] unless contraindicated **(AI)**
Hospitalized and Requires Oxygen Through a High-Flow Device or NIV	Use 1 of the following options: • **Dexamethasone (AI)** • **Dexamethasone plus remdesivir**[b] **(BIIb)** For patients with rapidly increasing oxygen needs and systemic inflammation, add either **baricitinib**[e] **(BIIa)** or **IV tocilizumab**[e] **(BIIa)** to 1 of the options above.[d,h]	For patients without evidence of VTE: • **Prophylactic dose** of heparin,[g] unless contraindicated **(AI)**
Hospitalized and Requires MV or ECMO	**Dexamethasone**[i] **(AI)** For patients who are within 24 hours of admission to the ICU: • **Dexamethasone plus IV tocilizumab (BIIa)** If IV tocilizumab is not available or not feasible to use, **IV sarilumab** can be used **(BIIa)**.	For patients without evidence of VTE: • **Prophylactic dose** of heparin,[g] unless contraindicated **(AI)** If patient is started on therapeutic heparin before transfer to the ICU, switch to a **prophylactic dose** of heparin, unless there is a non-COVID-19 indication **(BIII)**.

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

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] Corticosteroids that are prescribed for an underlying condition should be continued.

[b] If the patient progresses to requiring high-flow oxygen, NIV, MV, or ECMO, complete the full course of remdesivir (refer to Table A).

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[c] Evidence suggests that the benefit of remdesivir is greatest when the drug is given early in the course of COVID-19 (e.g., within 10 days of symptom onset). Clinical trials have not demonstrated a mortality benefit for remdesivir, but a large, placebo-controlled trial showed that the use of remdesivir reduced time to clinical recovery in hospitalized patients. See Rationale for the Use of Remdesivir below.

[d] Drugs are listed alphabetically. There are no studies that directly compare the use of baricitinib and tocilizumab, and there is insufficient evidence to recommend a drug or class of drug (i.e., JAK inhibitors, anti-IL-6 receptor mAbs) over the other. Treatment decisions should be based on local guidance, drug availability, and patient comorbidities.

[e] If baricitinib and IV tocilizumab are not available or not feasible to use, **tofacitinib** can be used instead of baricitinib **(BIIa)** and **IV sarilumab** can be used instead of IV tocilizumab **(BIIa)**.

[f] Contraindications for the use of therapeutic anticoagulation in patients with COVID-19 include platelet count <50 x 10^9/L, Hgb <8 g/dL, the need for dual antiplatelet therapy, bleeding within the last 30 days that required an ED visit or hospitalization, a history of a bleeding disorder, or an inherited or active acquired bleeding disorder. This list is based on the exclusion criteria from clinical trials; patients with these conditions have an increased risk of bleeding.

[g] Either LMWH or UFH heparin can be used. In general, LMWH is preferred.

[h] The Panel **recommends against** the use of **baricitinib** in combination with **tocilizumab** for the treatment of COVID-19, except in a clinical trial **(AIII)**. Because both baricitinib and tocilizumab are potent immunosuppressants, there is the potential for an additive risk of infection.

[i] The combination of **dexamethasone plus remdesivir** may be considered for patients who have recently been intubated **(CIII)**. The Panel **recommends against** the use of **remdesivir** monotherapy in these patients **(AIIa)**.

Key: ECMO = extracorporeal membrane oxygenation; ED = emergency department; Hgb = hemoglobin; ICU = intensive care unit; IL = interleukin; IV = intravenous; JAK = Janus kinase; LMWH = low-molecular-weight heparin; mAb = monoclonal antibody; MV = mechanical ventilation; NIV = noninvasive ventilation; the Panel = the COVID-19 Treatment Guidelines Panel; UFH = unfractionated heparin; ULN = upper limit of normal; VTE = venous thromboembolism

Table A. Dosing Regimens for the Drugs Recommended in Figure 2

Drug Name	Dosing Regimen	Comments
Remdesivir	RDV 200 mg IV once, then RDV 100 mg IV once daily for 4 days or until hospital discharge	• If the patient progresses to more severe illness, complete the course of RDV. • For a discussion on using RDV in patients with renal insufficiency, see Remdesivir.
Dexamethasone	DEX 6 mg IV or PO once daily for up to 10 days or until hospital discharge	• If DEX is not available, an equivalent dose of another corticosteroid may be used. • For more information, see Corticosteroids.
Baricitinib	Baricitinib dose is dependent on eGFR; duration of therapy is up to 14 days or until hospital discharge.	• eGFR ≥60 mL/min/1.73 m^2: Baricitinib 4 mg PO once daily • eGFR 30 to <60 mL/min/1.73 m^2: Baricitinib 2 mg PO once daily • eGFR 15 to <30 mL/min/1.73 m^2: Baricitinib 1 mg PO once daily • eGFR <15 mL/min/1.73 m^2: Baricitinib **is not recommended**.
Heparin	Therapeutic dose of SUBQ LMWH or IV UFH	• Administer for 14 days or until hospital discharge, unless there is a diagnosis of VTE or another indication for therapeutic anticoagulation.
	Prophylactic dose of SUBQ LMWH or SUBQ UFH	• Administer for the duration of the hospital stay.
Tofacitinib	Tofacitinib 10 mg PO twice daily for up to 14 days or until hospital discharge	• Use as an alternative immunomodulatory drug if baricitinib is not available or not feasible to use **(BIIa)**. • eGFR <60 mL/min/1.73 m^2: Tofacitinib 5 mg PO twice daily

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Drug Name	Dosing Regimen	Comments
Tocilizumab	Tocilizumab 8 mg/kg actual body weight (up to 800 mg) administered as a single IV dose	• In clinical trials, a third of the participants received a second dose of tocilizumab 8 hours after the first dose if no clinical improvement was observed.
Sarilumab	Use the single-dose, prefilled syringe (**not** the prefilled pen) for SUBQ injection. Reconstitute sarilumab 400 mg in 100 cc 0.9% NaCl and administer as an IV infusion over 1 hour.	• Use as an alternative immunomodulatory drug if tocilizumab is not available or not feasible to use **(BIIa)**. • In the United States, the currently approved route of administration for sarilumab is SUBQ injection. In the REMAP-CAP trial, the SUBQ formulation was used to prepare the IV infusion.
Key: DEX = dexamethasone; eGFR = estimated glomerular filtration rate; IV = intravenous; LMWH = low-molecular-weight heparin; NaCl = sodium chloride; PO = oral; RDV = remdesivir; SUBQ = subcutaneous; UFH = unfractionated heparin; VTE = venous thromboembolism		

Introduction

Two main processes are thought to drive the pathogenesis of COVID-19. Early in the clinical course, the disease is primarily driven by the replication of SARS-CoV-2. Subsequently, the disease appears to be also driven by a dysregulated immune/inflammatory response to SARS-CoV-2 that leads to tissue damage and thrombosis. Based on this understanding, therapies that directly target SARS-CoV-2 are anticipated to have the greatest effect early in the course of the disease, whereas immunosuppressive/anti-inflammatory/antithrombotic therapies are likely to be more beneficial after COVID-19 has progressed to stages characterized by hypoxemia.

Patients Who Do Not Require Supplemental Oxygen

Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of **dexamethasone (AIIa)** or **other corticosteroids (AIII)** for the treatment of COVID-19. Patients with COVID-19 who are receiving dexamethasone or another corticosteroid for an underlying condition should continue this therapy as directed by their health care provider.
- There is insufficient evidence to recommend either for or against the routine use of remdesivir for the treatment of patients who are hospitalized for COVID-19 who do not require supplemental oxygen. However, the use of remdesivir may be appropriate in patients who are at high risk of disease progression.

Rationale for Recommending Against the Use of Dexamethasone or Other Corticosteroids

In the RECOVERY trial, a multicenter, open-label trial in the United Kingdom, hospitalized patients with COVID-19 were randomized to receive dexamethasone plus standard of care or standard of care alone (control arm).[1] No survival benefit for dexamethasone was observed among the patients who did not require supplemental oxygen at enrollment: 17.8% of patients 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). See Table 4a 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 hospitalized patients who do not require supplemental oxygen, unless the patient has another indication for corticosteroid therapy.

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Rationale for Determining That There Is Insufficient Evidence to Recommend Either for or Against the Use of Remdesivir

ACTT-1 was a multinational randomized controlled trial that compared intravenous (IV) 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 subgroup.[2]

In a manufacturer-sponsored, open-label randomized trial that included 596 patients with moderate COVID-19, patients who received 5 days of remdesivir had higher odds of a better clinical status on Day 11 (based on a 7-point ordinal scale) than those who received standard of care (OR 1.65; 95% CI, 1.09–2.48; $P = 0.02$).[3]

The Solidarity trial was a large, multinational, open-label randomized controlled trial that compared a 10-day course of remdesivir to standard of care. About 25% of hospitalized patients in both arms did not require supplemental oxygen at study entry. The primary endpoint of in-hospital mortality occurred in 11 of 661 patients (2%) in the remdesivir arm and 13 of 664 patients (2.1%) in the control arm (rate ratio 0.90; 99% CI, 0.31–2.58).[4] Please see Table 2a for more information.

Data from the PINETREE trial showed a clinical benefit for early treatment with remdesivir in nonhospitalized patients with COVID-19 who had a high risk of clinical progression. Patients were randomized to receive 3 days of IV remdesivir or placebo. The median duration of symptoms was 5 days at treatment initiation. By Day 28, there was a significant decrease in the proportion of patients who were hospitalized and/or died in the remdesivir arm: this primary endpoint occurred in 0.7% of remdesivir recipients and in 5.3% of placebo recipients (HR 0.13; 95% CI, 0.03–0.59; $P = 0.008$).[5]

Because these trials produced conflicting results regarding the benefits of remdesivir, the Panel finds the available evidence insufficient to recommend either for or against routine treatment with remdesivir for all hospitalized patients with moderate COVID-19. However, the Panel recognizes that clinicians may decide that remdesivir is appropriate for certain hospitalized patients with moderate disease (e.g., those who have a particularly high risk for clinical progression).

Patients Who Require Supplemental Oxygen

Patients who require supplemental oxygen, but not high-flow oxygen, noninvasive ventilation (NIV), or mechanical ventilation are a heterogeneous group. Some of these patients will have mild disease that will improve after a short period with or without treatment with remdesivir, dexamethasone, or both; others will develop progressive disease despite treatment and require a more intensive level of care. There is no consensus on which clinical or laboratory parameters allow for reliable risk-stratification to guide therapy and/or identify which subsets of patients will experience progressive lung injury and hypoxemia.

Some studies have tried to define this group according to traditional risk factors for COVID-19 progression and/or by the presence of elevated inflammatory markers like C-reactive protein (CRP), but evidence to support a specific identifying biomarker or clinical threshold is lacking.

Recommendations

- The Panel recommends using 1 of the following options for hospitalized patients who require supplemental oxygen:
  - **Remdesivir** (e.g., for patients who require minimal supplemental oxygen) **(BIIa)**
  - **Dexamethasone plus remdesivir (BIIb)**

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- **Dexamethasone (BI)**; for patients on dexamethasone who have rapidly increasing oxygen needs and systemic inflammation, add a second immunomodulatory drug (e.g., **tocilizumab** or **baricitinib**) **(CIIa)**

- If dexamethasone is not available, an alternative corticosteroid (e.g., **prednisone**, **methylprednisolone**, or **hydrocortisone**) can be used **(BIII)**. See Corticosteroids for dosing recommendations.
- For nonpregnant patients, the Panel recommends using a **therapeutic dose** of heparin for patients who have D-dimer levels above the upper limit of normal (ULN), require low-flow oxygen, and have no increased bleeding risk **(CIIa)**. Low-molecular-weight heparin (LMWH) is preferred over unfractionated heparin.

Rationale for the Use of Remdesivir

In the ACTT-1 trial, remdesivir was associated with improved time to recovery in the 435 patients who required oxygen supplementation but not high-flow oxygen, NIV, or mechanical ventilation (7 days for remdesivir vs. 9 days for placebo; recovery rate ratio 1.45; 95% CI, 1.18–1.79). Fewer patients in the remdesivir arm than in the placebo arm progressed to requiring high-flow oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) (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).[2]

The Solidarity 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 for death in the overall study population 0.95; 95% CI, 0.81–1.11; rate ratio for death in patients who did not require mechanical ventilation at entry 0.86; 99% CI, 0.67–1.11). There was no difference between patients who received remdesivir and those who received standard of care in the percentage of those who progressed to mechanical ventilation (11.9% vs. 11.5%) or in length of hospital stay.[4] However, an open-label trial like Solidarity is less well-suited to assess time to recovery than a placebo-controlled trial. In the Solidarity trial, because both clinicians and patients knew that remdesivir was being administered, it is possible that hospital discharge was delayed in order to complete the 10-day course of therapy.

DisCoVeRy was a multinational, open-label randomized controlled trial that compared up to 10 days of remdesivir plus standard of care to standard of care alone in hospitalized patients with moderate or severe COVID-19. There was no significant difference in the odds of improved clinical status by Day 15 between the patients in the remdesivir arm and the standard of care arm (OR 0.98; 95% CI, 0.77–1.25). At Day 28, there were also no differences between the arms in either mortality (8% in remdesivir arm vs. 9% in standard of care arm) or clinical status. The DisCoVeRy trial shared with the Solidarity trial the major limitation of open-label design. Additionally, 440 of the 832 participants in the DisCoVeRy trial (219 in the remdesivir arm and 221 in the standard of care arm) were also Solidarity trial participants.[6]

Although the open-label Solidarity and DisCoVeRy trials demonstrated no mortality benefit for remdesivir, in ACTT-1, a large randomized placebo-controlled trial, remdesivir significantly reduced time to clinical recovery. In a post hoc analysis, this clinical benefit of remdesivir was most evident in those who had symptoms for ≤10 days. The evidence from the ACTT-1 and PINETREE trials suggests that remdesivir will have its greatest impact when administered early in the clinical course, which is also the case for antiviral agents used to treat other viral infections.[5] The Panel recommends **remdesivir** (without dexamethasone) as a treatment option for certain patients with COVID-19 who require minimal supplemental oxygen and are in the early course of the disease **(BIIa)**. In these individuals, the hyperinflammatory state where corticosteroids might be most beneficial may not yet be present or fully developed.

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Although several trials studied a 10-day course of remdesivir,[2,4] a 5-day course has been shown to be comparable to 10 days of therapy in hospitalized patients with moderate to severe COVID-19.[3,7] For more information, please see Table 2a.

Rationale for the Use of Remdesivir Plus Dexamethasone

The safety and efficacy of using a combination of remdesivir and corticosteroids have primarily been evaluated in observational studies. Some of these studies have suggested that there is a clinical benefit of using remdesivir plus dexamethasone.[8-10] Remdesivir plus dexamethasone has not been directly compared to dexamethasone alone in a large randomized clinical trial. 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 the theoretical combined benefit of antiviral and anti-inflammatory therapies, the Panel recommends the combination of **dexamethasone plus remdesivir** as a treatment option for patients who require supplemental oxygen **(BIIb)**, despite important limitations of observational data.

Rationale for the Use of Dexamethasone

In the RECOVERY trial, treatment with dexamethasone conferred a survival benefit among patients who required supplemental oxygen at enrollment. Fewer patients in the dexamethasone arm than in the standard of care arm died within 28 days of enrollment (23.3% vs. 26.2%; rate ratio 0.82; 95% CI, 0.72–0.94).[1] However, the amount of supplemental oxygen that patients were receiving and the proportions of patients who required oxygen through a high-flow device or NIV 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, see Corticosteroids.

Some experts prefer not to use dexamethasone monotherapy in patients who require supplemental oxygen because of the theoretical concern that corticosteroids might slow viral clearance when 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.[11-13] Some studies have suggested that corticosteroids slow SARS-CoV-2 clearance, but the results to date are inconclusive.[14-18]

Rationale for Adding a Second Immunomodulatory Drug to Dexamethasone in Certain Patients Who Require Rapidly Increasing Oxygen Supplementation

Several major randomized trials that evaluated the use of interleukin (IL)-6 inhibitors or Janus Kinase (JAK) inhibitors with or without corticosteroids in patients with COVID-19 have included patients who required only low-flow supplemental oxygen. However, subgroup analyses in these trials have not clearly defined which patients in this heterogeneous group are most likely to benefit from using corticosteroids with another immunomodulator. Direct comparison between trials is not possible because background therapies (e.g., corticosteroids) and inclusion criteria (e.g., the requirement for elevated inflammatory markers) differed between trials. Nonetheless, some trials suggest that adding a second immunomodulator to dexamethasone provides benefits in patients who require low-flow supplemental oxygen.[19-21] The RECOVERY trial showed that in a subgroup of patients that included patients on low-flow oxygen, those who received tocilizumab plus dexamethasone had a lower incidence of 28-day mortality than those who received usual care (which included dexamethasone).[19] Similarly, data on JAK inhibitors are also inconclusive; for example, the COV-BARRIER trial did not find a statistically significant benefit

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for baricitinib in patients on low-flow oxygen,[20] whereas the placebo-controlled STOP-COVID trial demonstrated a reduction in the incidence of respiratory failure or death in the subgroup of patients on low-flow oxygen who received tofacitinib.[21]

Given the uncertainty concerning which patients in this group would benefit from adding a second immunomodulator (e.g., baricitinib, tocilizumab) to dexamethasone treatment, the Panel recommends considering these therapies on a case-by-case basis for individuals with rapidly increasing oxygen requirements and elevated markers of systemic inflammation **(CIIa)**. Because there are no studies that directly compare the use of baricitinib and tocilizumab as treatments for COVID-19, the Panel has insufficient evidence to recommend 1 drug over the other. Treatment decisions should be based on local guidance, drug availability, and patient comorbidities.

Additional Considerations

- Baricitinib or tocilizumab should only be given in combination with dexamethasone or another corticosteroid. Some clinicians may assess a patient's clinical response to dexamethasone before deciding whether adding baricitinib or tocilizumab as a second immunomodulatory drug is necessary.
- Because there are no studies that directly compare the use of baricitinib and tocilizumab as treatments for COVID-19, the Panel has insufficient evidence to recommend 1 drug or class of drugs (i.e., JAK inhibitors, anti-IL-6 receptor mAbs) over the other. Treatment decisions should be based on local guidance, drug availability, and patient comorbidities.
- If baricitinib and IV tocilizumab are not available or not feasible to use, **tofacitinib** can be used instead of baricitinib **(BIIa)** and **IV sarilumab** can be used instead of IV tocilizumab **(BIIa)**.
- The Panel **recommends against** the use of **baricitinib** in combination with tocilizumab for the treatment of COVID-19, except in a clinical trial **(AIII)**. Because both baricitinib and tocilizumab are potent immunosuppressants, there is the potential for an additive risk of infection.
- Combination immunosuppressive therapy (e.g., dexamethasone with baricitinib or tocilizumab) may increase the risk of opportunistic infections or reactivation of latent infections; however, randomized trials to date have not demonstrated an increase in the frequency of infections.
- Cases of severe and disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with tocilizumab and corticosteroids.[22,23] Many clinicians would initiate empiric treatment for strongyloidiasis (e.g., with the antiparasitic drug ivermectin) with or without serologic testing in patients from areas where *Strongyloides* is endemic (i.e., tropical, subtropical, or warm temperate areas).

Rationale for Using a Therapeutic Dose of Heparin in Certain Patients

Three open-label randomized controlled trials compared the use of therapeutic doses of heparin to prophylactic or intermediate doses of heparin in hospitalized patients who did not require intensive care unit (ICU)-level care. The entry criteria into these studies varied, but they typically included those who required supplemental oxygen, had elevated D-dimer levels, and were not at risk of major bleeding events.

The largest multiplatform trial (ATTACC/ACTIV-4a/REMAP-CAP) showed an increase in the number of organ support-free days in the therapeutic heparin arm, but no difference in mortality or length of hospitalization.[24] The RAPID trial enrolled patients with elevated D-dimer levels and hypoxemia. The patients were randomized to receive therapeutic or prophylactic doses of heparin. There was no statistically significant difference between the arms in the occurrence of the primary endpoint (a

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composite of ICU admission, receipt of NIV or mechanical ventilation, or death by Day 28), but the use of therapeutic heparin reduced 28-day mortality.[25] The HEP-COVID trial enrolled patients who required supplemental oxygen and who had D-dimer levels that were >4 times the ULN or a sepsis-induced coagulopathy score of ≥4. The primary endpoint (a composite of venous thromboembolism [VTE], arterial thromboembolism, and death by Day 30) occurred significantly less frequently in patients who received therapeutic LMWH than in those who received prophylactic LMWH, but there was no difference in mortality by Day 30 between the arms.[26] The results from smaller randomized trials, single-center trials, and observational studies have also been published.

Based on the available data, the Panel recommends using a **therapeutic dose** of heparin for patients who have D-dimer levels above the ULN, require low-flow oxygen, and have no increased bleeding risk **(CIIa)**. The rating reflects the fact that, although the 3 randomized controlled trials showed a clinical benefit for therapeutic heparin in hospitalized patients, the inclusion criteria and the beneficial outcomes differed between the trials. In addition, it should be noted that <20% of patients who were screened for these studies were enrolled; therefore, these data may not be generalizable to all hospitalized patients with COVID-19.

Patients Who Require Oxygen Through a High-Flow Device or Noninvasive Ventilation

Recommendations

- The Panel recommends using 1 of the following options for hospitalized patients who require oxygen through a high-flow device or NIV:
  - **Dexamethasone (AI)**
  - **Dexamethasone plus remdesivir (BIIb)**
- For patients who have rapidly increasing oxygen needs and have increased markers of inflammation, add either **baricitinib (BIIa)** or **tocilizumab (BIIa)** (drugs are listed alphabetically) to 1 of the options above.
- The Panel recommends using a **prophylactic dose** of heparin as VTE prophylaxis, unless a contraindication exists **(AI)**.
- For patients who are started on a therapeutic dose of heparin in a non-ICU setting due to COVID-19 and then transferred to the ICU, the Panel recommends switching from the therapeutic dose to a **prophylactic dose** of heparin, unless VTE is confirmed **(BIII)**.
- The Panel **recommends against** the use of an **intermediate dose** (e.g., enoxaparin 1 mg/kg once daily) or a **therapeutic dose** of anticoagulation for VTE prophylaxis, except in a clinical trial **(BI)**.

Additional Considerations

- If dexamethasone is not available, an equivalent dose of another corticosteroid (e.g., **prednisone**, **methylprednisolone**, or **hydrocortisone**) may be used **(BIII)**. See Corticosteroids for more information.
- Immunosuppressive therapy (e.g., dexamethasone with or without baricitinib or tocilizumab) may increase the risk of opportunistic infections or reactivation of latent infections; however, randomized trials to date have not demonstrated an increase in the frequency of infections.
- Cases of severe and disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with tocilizumab and corticosteroids.[22,23] Many clinicians would initiate empiric treatment for strongyloidiasis (e.g., with the antiparasitic drug ivermectin) with or without

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serologic testing in patients from areas where *Strongyloides* is endemic (i.e., tropical, subtropical, or warm temperate areas).

Rationale for the Use of Dexamethasone

In the RECOVERY trial, treatment with dexamethasone conferred a survival benefit among patients who required supplemental oxygen without mechanical ventilation at enrollment: 23.3% of the patients in the dexamethasone arm versus 26.2% in the standard of care arm died within 28 days of enrollment (rate ratio 0.82; 95% CI, 0.72–0.94).[1]

Rationale for the Use of Remdesivir Plus Dexamethasone

The safety and efficacy of using a combination of remdesivir and corticosteroids have primarily been evaluated in observational studies. Some of these studies have suggested that there is a clinical benefit of using remdesivir plus dexamethasone.[8-10] Remdesivir plus dexamethasone has not been directly compared to dexamethasone alone in a large randomized clinical trial. 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 the theoretical combined benefit of antiviral and anti-inflammatory therapies, the Panel recommends the combination of **dexamethasone plus remdesivir** as a treatment option for patients who require high-flow oxygen or NIV **(BIIb)**, despite the limitations of observational data.

Rationale for Not Recommending Remdesivir Monotherapy

In the ACTT-1 trial, there was no observed difference in time to recovery between the remdesivir and placebo arms in the subgroup of 193 patients who required high-flow oxygen or NIV at enrollment (recovery rate ratio 1.09; 95% CI, 0.76–1.57). A post hoc analysis did not show a survival benefit for remdesivir at Day 29, but the trial was not powered to detect this difference.[2] The Panel **does not recommend** using **remdesivir monotherapy** in patients who require high-flow oxygen or NIV because there is uncertainty regarding whether remdesivir alone confers a clinical benefit in this subgroup **(AIIa)**. Dexamethasone alone or remdesivir plus dexamethasone are better treatment options for COVID-19 in this group of patients.

Patients who start remdesivir monotherapy and then progress to requiring dexamethasone and oxygen through a high-flow device or NIV should continue to receive 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 Adding a Second Immunomodulatory Drug to Dexamethasone in Certain Hospitalized Patients

Data from several large clinical trials suggest that adding a second immunomodulatory drug, such as baricitinib or tocilizumab, to dexamethasone provides a clinical benefit in patients who require oxygen supplementation through a high-flow device or NIV.

The REMAP-CAP and RECOVERY trials, the 2 largest randomized controlled trials of tocilizumab to date, have both reported a mortality benefit for tocilizumab among patients with rapid respiratory decompensation who require oxygen delivery through a high-flow device or NIV.[19,27] Most patients in

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both studies received corticosteroids.

In the REMAP-CAP trial, patients who were admitted to an ICU with severe to critical COVID-19 and rapid respiratory decompensation were randomized to receive open-label tocilizumab or usual care. The use of tocilizumab reduced in-hospital mortality (28% of patients died in the tocilizumab arm vs. 36% in the usual care arm) and, during 21 days of follow-up, increased the median number of days free of respiratory and cardiovascular organ support (10 days in the tocilizumab arm vs. 0 days in the usual care arm; OR 1.64; 95% CI, 1.25–2.14). Enrollment occurred within 24 hours of ICU admission and within a median of 1.2 days of hospitalization (IQR 0.8–2.8 days), suggesting that tocilizumab confers a benefit to patients experiencing rapid respiratory decompensation. The RECOVERY trial also suggested a mortality benefit for tocilizumab plus dexamethasone in a subset of patients that included those who required NIV or high-flow oxygen. In this study, a subset of patients with hypoxemia and CRP ≥75 mg/L were randomized to receive tocilizumab or usual care. Tocilizumab reduced all-cause mortality in these patients; by Day 28, 29% of patients in the tocilizumab arm versus 33% in the usual care arm had died (rate ratio 0.86; 95% CI, 0.77–0.96).

In the COV-BARRIER trial, 1,525 hospitalized patients with COVID-19 and ≥1 elevated inflammatory biomarker were randomized 1:1 to receive baricitinib 4 mg orally or placebo in addition to the local standard of care for up to 14 days (or until hospital discharge).[20] Overall, there was no difference in the occurrence of the primary endpoint of progression to high-flow oxygen, NIV, mechanical ventilation, or death by Day 28 between the baricitinib arm (27.8% of patients) and the placebo arm (30.5% of patients; OR 0.85; 95% CI, 0.67–1.08; $P = 0.18$). However, all-cause mortality by Day 28 was 8.1% in the baricitinib arm and 13.1% in the placebo arm, resulting in a 38.2% reduction in mortality for patients who received baricitinib (HR 0.57; 95% CI, 0.41–0.78; nominal $P = 0.002$). The difference in mortality was most pronounced in the subgroup of 370 patients receiving high-flow oxygen or NIV at baseline (17.5% in the baricitinib arm vs. 29.4% in the placebo arm; HR 0.52; 95% CI, 0.33–0.80; nominal $P = 0.007$). The occurrence of adverse events, serious adverse events, serious infections, and VTE events in the arms was comparable.

The ACTT-2 trial demonstrated that baricitinib used in combination with remdesivir improved time to recovery in hospitalized patients with COVID-19. The effect was most pronounced in patients who were receiving high-flow oxygen or NIV. However, patients receiving corticosteroids were excluded from the ACTT-2 trial, limiting the generalizability of these findings.

Given the clinical trial data (see Table 4e), the Panel recommends adding **baricitinib** or **tocilizumab** as a second immunomodulatory treatment in combination with dexamethasone for patients who are receiving oxygen supplementation through a high-flow device or NIV **(BIIa)**.

Additional Considerations

- Baricitinib or tocilizumab should only be given in combination with dexamethasone or another corticosteroid. Some clinicians may assess a patient's clinical response to dexamethasone before deciding whether adding baricitinib or tocilizumab is necessary.
- Studies that directly compare baricitinib to tocilizumab as treatments for COVID-19 are not available. Therefore, there is insufficient evidence for the Panel to recommend 1 drug over the other. Treatment decisions should be based on local guidance, drug availability, and patient comorbidities.
- If baricitinib and IV tocilizumab are not available or not feasible to use, **tofacitinib** can be used instead of baricitinib **(BIIa)** and **IV sarilumab** can be used instead of IV tocilizumab **(BIIa)**.
- Although approximately one third of patients in the REMAP-CAP and RECOVERY trials

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received a second dose of tocilizumab at the discretion of their treating physician, data on outcomes based on receipt of 1 or 2 doses is not available. Therefore, there is insufficient evidence to determine which patients, if any, would benefit from an additional dose of the drug.

Rationale for Recommending Against the Use of the Combination of Baricitinib and Tocilizumab

The Panel **recommends against** the use of the combination of **baricitinib** and **tocilizumab** for the treatment of COVID-19 (except in a clinical trial) because there is insufficient evidence for the use of this combination **(AIII)**. Given that both baricitinib and tocilizumab are potent immunosuppressants, there is the potential for an additive risk of infection.

Rationale for Recommending Sarilumab and Dexamethasone as an Alternative to Tocilizumab and Dexamethasone in Certain Hospitalized Patients

In an updated report from the REMAP-CAP trial, the efficacy of tocilizumab and sarilumab in improving survival and reducing the duration of organ support was similar. Compared to noncontemporary control patients who received placebo plus dexamethasone, patients who received sarilumab and dexamethasone demonstrated reduced in-hospital mortality, shorter time to ICU discharge, and more organ support-free days.[28] Administering sarilumab in combination with dexamethasone (n = 483) was noninferior to tocilizumab with dexamethasone (n = 943) with regard to the number of organ support-free days and mortality.

Even though the REMAP-CAP trial reported that sarilumab and tocilizumab have similar efficacy in the treatment of hospitalized patients with COVID-19, the Panel recommends using **sarilumab** only when **tocilizumab** is not available or is not feasible to use **(BIIa)**. The evidence of efficacy for tocilizumab is more extensive than the evidence for sarilumab; in addition, sarilumab is currently only approved for use as a subcutaneous (SUBQ) injection in the United States.

In 1 of the clinical trials, a single dose of sarilumab 400 mg for SUBQ injection was reconstituted in 50 mL or 100 mL of normal saline and administered as an IV infusion over 1 hour.

Rationale for Recommending the Use of Tofacitinib Plus Dexamethasone in Certain Hospitalized Patients

In the STOP-COVID trial, a double-blind randomized placebo-controlled trial, use of tofacitinib was associated with a decreased risk of respiratory failure and death (risk ratio 0.63; 95% CI, 0.41–0.97). All-cause mortality within 28 days was 2.8% in the tofacitinib arm (n = 144) and 5.5% in the placebo arm (n = 145) (HR 0.49; 95% CI, 0.15–1.63). Approximately 80% of patients in each arm also received corticosteroids.[21]

Data from the STOP-COVID trial supports the idea that tofacitinib plus steroids improves outcomes in hospitalized patients with COVID-19. Both baricitinib and tofacitinib belong to the same class of anti-inflammatory drugs (kinase inhibitors) and have overlapping mechanisms of action. The Panel recommends using **tofacitinib** as an alternative to **baricitinib** only when baricitinib is not available or not feasible to use because the evidence of efficacy for tofacitinib is less extensive than the evidence for baricitinib **(BIIa)**.

Rationale for the Use of Prophylactic Doses of Heparin

The INSPIRATION trial compared the use of intermediate doses of anticoagulation (enoxaparin 1 mg/kg SUBQ once daily; n = 299) to prophylactic doses of anticoagulation (enoxaparin 40 mg SUBQ once daily; n = 299) in adults who were admitted to the ICU with COVID-19.[29] Among these patients, 34.3%

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received oxygen delivery using high-flow oxygen or NIV. The primary endpoint in this study was a composite of adjudicated VTE, arterial thrombosis, ECMO, or all-cause mortality. The primary endpoint occurred in 45.7% of patients who received the intermediate dose and in 44.1% of patients who received the prophylactic dose (OR 1.06; 95% CI, 0.76–1.48). Overall, there was no significant benefit of using this intermediate dose of anticoagulation in these ICU patients with COVID-19.

The multiplatform randomized controlled trial REMAP-CAP/ACTIV-4a/ATTACC also compared the effectiveness of using a therapeutic dose of heparin or LMWH to standard of care in critically ill patients with COVID-19; 65% of these patients received high-flow oxygen or NIV.[30] The trial was stopped for futility after 536 patients were randomized to receive therapeutic anticoagulation and 564 patients were randomized to receive standard of care. The median number of organ support-free days was 3 days (IQR -1 to 16 days) in patients who received the therapeutic dose of anticoagulation and 4 days (IQR -1 to 16 days) in patients who received standard of care (adjusted OR 0.83; 95% CrI, 0.67–1.03; posterior probability of futility [OR < 1.2] 99.9%). The proportion of patients who survived to hospital discharge did not differ between the arms (62.7% of patients in the therapeutic dose arm vs. 64.5% in the standard of care arm; OR 0.84; 95% CrI, 0.64–1.11). No significant benefit was reported for the use of a therapeutic dose of heparin in patients with COVID-19 who were admitted to the ICU.

Patients Who Require Mechanical Ventilation or Extracorporeal Membrane Oxygenation

Recommendations

- The Panel recommends using **dexamethasone** for hospitalized patients with COVID-19 who require mechanical ventilation or ECMO **(AI)**.
- The Panel recommends using **dexamethasone plus tocilizumab** for patients with COVID-19 who are within 24 hours of admission to the ICU **(BIIa)**.
- The Panel recommends using a **prophylactic dose** of heparin as VTE prophylaxis, unless a contraindication exists **(AI)**.
- The Panel **recommends against** the use of an **intermediate dose** (e.g., **enoxaparin** 1 mg/kg once daily) or a **therapeutic dose** of anticoagulation for VTE prophylaxis, except in a clinical trial **(BI)**.
- For patients who are started on a therapeutic dose of heparin in a non-ICU setting due to COVID-19 and then transferred to the ICU, the Panel recommends switching from the therapeutic dose to a **prophylactic dose** of heparin, unless there is a non-COVID-19 indication **(BIII)**.

Additional Considerations

- If dexamethasone is not available, an equivalent dose of an alternative corticosteroid (e.g., **prednisone**, **methylprednisolone**, **hydrocortisone**) may be used **(BIII)**.
- For patients who initially received remdesivir monotherapy and progressed to requiring mechanical ventilation or ECMO, dexamethasone should be initiated and remdesivir should be continued until the treatment course is completed.
- The Panel **recommends against** the initiation of **remdesivir monotherapy** in patients who require mechanical ventilation or ECMO **(AIIa)**.
- Tocilizumab should be given only in combination with dexamethasone (or another corticosteroid at an equivalent dose).
- Although some patients in the REMAP-CAP and RECOVERY trials received a second dose of tocilizumab at the discretion of their treating physician, there is insufficient evidence to determine which patients, if any, would benefit from an additional dose of the drug.

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- The combination of dexamethasone and tocilizumab may increase the risk of opportunistic infections or reactivation of latent infections. Prophylactic treatment for strongyloidiasis (e.g., with the antiparasitic drug ivermectin) should be considered for patients who are from areas where *Strongyloides* is endemic.

Rationale for the Use of Dexamethasone Monotherapy

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

Dexamethasone reduces mortality in critically ill patients with COVID-19 according to a meta-analysis that aggregated 7 randomized trials and included data on 1,703 critically ill patients.[31] The largest trial in the meta-analysis was the RECOVERY trial, whose subgroup of mechanically ventilated patients was included.[1] For details about the meta-analysis and the RECOVERY trial, see Corticosteroids and Table 4a. Because the benefits of dexamethasone outweigh the potential harms, the Panel recommends using **dexamethasone** in hospitalized patients with COVID-19 who require 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. However, there is a theoretical reason to administer dexamethasone plus remdesivir to 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.[11,12]

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 patients with nonsevere COVID-19 suggested that viral clearance was delayed in those who received corticosteroids,[32] 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.[18] Given the conflicting results from observational studies and the lack 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 dexamethasone and remdesivir due to uncertainties about the benefit of using remdesivir in critically ill patients.

Rationale for Recommending the Use of Tocilizumab Plus Dexamethasone in Patients Within 24 Hours of Admission to the Intensive Care Unit

The REMAP-CAP and RECOVERY trials, the 2 largest randomized controlled trials of tocilizumab to date, both reported a mortality benefit for tocilizumab in patients who experienced rapid respiratory decompensation and were recently admitted to the ICU, including those who required mechanical ventilation.[19,27] The REMAP-CAP trial enrolled patients within 24 hours of admission to the ICU. Previous trials that enrolled patients later in the course of ICU care and/or who received oxygen support >24 hours after ICU admission have failed to show consistent clinical benefits for tocilizumab (see Table 4e). Thus, it is unclear whether there is a clinical benefit for tocilizumab in patients who received mechanical ventilation for >24 hours. Findings from the RECOVERY trial suggest a clinical benefit for tocilizumab plus corticosteroids among patients with rapid clinical progression who received mechanical ventilation. Please see the Rationale for Adding a Second Immunomodulatory Drug to Dexamethasone in Certain Hospitalized Patients section above for additional details on the clinical trial data and rationale for using tocilizumab in this situation.

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Rationale for Recommending Against the Use of Remdesivir Monotherapy

A clear benefit of remdesivir monotherapy has not been demonstrated in patients who require mechanical ventilation or ECMO. In the ACTT-1 trial, remdesivir did not improve the recovery rate in this subgroup of patients (recovery rate ratio 0.98; 95% CI, 0.70–1.36), and in a post hoc analysis of deaths by Day 29, remdesivir did not improve survival in this subgroup (HR 1.13; 95% CI, 0.67–1.89).[2] In the Solidarity trial, there was a trend toward increased mortality among patients who received mechanical ventilation and were randomized to receive remdesivir rather than standard of care (rate ratio 1.27; 95% CI, 0.99–1.62).[4] 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 mechanical ventilation or ECMO, remdesivir should be continued until the treatment course is completed. Clinical trials that evaluated remdesivir categorized patients based on their severity of illness at study enrollment; 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.

Rationale for Recommending the Use of Sarilumab and Dexamethasone as an Alternative to Tocilizumab and Dexamethasone in Certain Hospitalized Patients

Please refer to the Patients Who Require Oxygen Through a High-Flow Device or Noninvasive Ventilation section above for the rationale regarding the use of sarilumab and dexamethasone as an alternative to tocilizumab and dexamethasone in certain hospitalized patients.

Rationale for Determining That There is Insufficient Evidence to Recommend the Use of Baricitinib in Addition to Standard of Care in Mechanically Ventilated Individuals

A cohort of critically ill patients was added to the COV-BARRIER trial after the completion of the original study. The results for the cohort were not included in the primary results of the main trial.[33] In this addendum, 101 patients on mechanical ventilation or ECMO were randomized 1:1 to receive baricitinib 4 mg (n = 51) or placebo (n = 50) for up to 14 days in combination with standard of care. Baricitinib significantly reduced 28-day all-cause mortality (39.2% in the baricitinib arm vs. 58.0% in the placebo arm; HR 0.54; 95% CI, 0.31–0.96; $P = 0.030$). However, given the small sample size, the Panel considers the evidence insufficient to issue a recommendation for patients on mechanical ventilation or ECMO.

Rationale for the Use of Prophylactic Doses of Heparin

Patients who required mechanical ventilation and ECMO were included in the multiplatform REMAP-CAP/ACTIV-4a/ATTACC trial and INSPIRATION trial.[29,30] Based on the results of these trials, the recommendations for using prophylactic doses of heparin in hospitalized, nonpregnant patients who require mechanical ventilation or ECMO are the same as those for patients who require oxygen through a high-flow device or NIV.

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Therapeutic Management of Hospitalized Pediatric Patients With Multisystem Inflammatory Syndrome in Children (MIS-C) (With Discussion on Multisystem Inflammatory Syndrome in Adults [MIS-A])

Last Updated: February 24, 2022

This section outlines the COVID-19 Treatment Guidelines Panel's (the Panel) recommendations for the therapeutic management of pediatric patients with multisystem inflammatory syndrome in children (MIS-C). The Centers for Disease Control and Prevention's (CDC) case definition for MIS-C includes "an individual aged <21 years."[1] The recommendations in this section encompass this age group. There are no randomized controlled trials that compare treatment approaches for MIS-C. However, data from descriptive and observational comparative effectiveness studies are available to guide treatment for MIS-C. For information on the clinical manifestations of MIS-C, see Special Considerations in Children.

Multisystem Inflammatory Syndrome in Adults

It should be noted that adults can present with a syndrome similar to MIS-C, termed multisystem inflammatory syndrome in adults (MIS-A).[2] The published literature on MIS-A is restricted to small case series that provide little data to guide treatment decisions for patients with MIS-A.[3] Although Panel members extrapolate from MIS-C data to aid in the management of individuals with MIS-A, it should be emphasized that this approach to managing MIS-A has not been studied.

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Figure 3. Therapeutic Management of Hospitalized Pediatric Patients With MIS-C

PANEL'S RECOMMENDATIONS

MIS-C

Initial treatment for MIS-C includes both immunomodulatory and antithrombotic therapy.

Initial Immunomodulatory Therapy:

- **IVIG** 2 g/kg IBW/dose (up to a maximum total dose of 100 g)[a] IV **plus** low-to-moderate dose **methylprednisolone** (1–2 mg/kg/day) IV[a] or another glucocorticoid at an equivalent dose[a] **(AIIb)**.
- The Panel recommends against the routine use of IVIG monotherapy for the treatment of MIS-C unless glucocorticoid use is contraindicated **(AIIb)**.

Intensification Immunomodulatory Therapy:

- For children with refractory MIS-C who do not improve within 24 hours of initial immunomodulatory therapy, start 1 of the following (listed in alphabetical order) **(AIII)**:
  - High-dose **anakinra** 5–10 mg/kg IV or SUBQ daily **(BIIb)**, *or*
  - **Higher-dose glucocorticoid** (e.g., **methylprednisolone** 10–30 mg/kg/day IV or equivalent glucocorticoid) **(BIIb),**[b] *or*
  - **Infliximab**[c] 5–10 mg/kg IV for 1 dose **(BIIb).**

Antithrombotic Treatment:

- Low-dose **aspirin** (3–5 mg/kg/day, up to maximum daily dose of 81 mg) PO for all patients without risk factors for bleeding **(AIII)**, **AND**
- Anticoagulation for patients who fall under 1 of the following clinical scenarios:
  - **Therapeutic anticoagulation** for patients with large CAAs according to the American Heart Association guidelines for Kawasaki disease **(AIII)**.
  - **Therapeutic anticoagulation** for patients with moderate to severe LV dysfunction who have no risk factors for bleeding **(AIII)**.
  - For patients with MIS-C who do not have large CAAs or moderate to severe LV dysfunction, consider **prophylactic or therapeutic anticoagulation** on an individual basis, taking into consideration risk factors for thrombosis. See below for additional information.

Rating of Recommendations: A = Strong; B = Moderate; C = Weak
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] Duration of therapy may vary. See duration in table and text below.

[b] In certain patients with severe illness, intensification therapy may include dual therapy with higher-dose glucocorticoids and infliximab or anakinra. Anakinra and infliximab **should not be given** in combination.

[c] Infliximab **should not be used** in patients with macrophage activation syndrome.

Key: CAA = coronary artery aneurysm; IBW = ideal body weight; IV = intravenous; IVIG = intravenous immunoglobulin; LV = left ventricular; MIS-C = multisystem inflammatory syndrome in children; PO = oral; SUBQ = subcutaneously

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Table A. Dosing Regimens for the Drugs Recommended for the Treatment of MIS-C

Drug Name	Dosing Regimens *For infants, children, and adolescents unless otherwise specified. The doses listed are for FDA-approved indications for other diseases or from reported experiences or clinical trials.*	Adverse Events	Monitoring Parameters
Intravenous Immunoglobulin	• IVIG 2 g/kg IBW/dose (up to a maximum total dose of 100 g) IV for 1 dose • In the event of cardiac dysfunction or fluid overload, consider administering IVIG in divided doses (1 g/kg IBW/dose IV every 24 hours for 2 doses).	• Hypersensitivity • Fever • Chills • Flushing • Hemolytic anemia	• Renal function • Urine output • CBC with differential • Infusion or injection-related AE • Anaphylaxis • Signs and symptoms of hemolysis
Methyl-prednisolone	• Methylprednisolone 1 to 2 mg/kg/dose IV every 12 hours • If the patient with MIS-C does not respond to 1–2 mg/kg/dose IV every 12 hours, increase the dose to 10–30 mg/kg/day (up to maximum of 1,000 mg/day) IV for 1 to 3 days.	• Adrenal suppression • Hyperglycemia • Sodium retention • Fluid retention • Leukocytosis • Immune suppression	• Blood pressure • CBC with differential • BMP
Anakinra	Anakinra 5–10 mg/kg/day IV (preferred) or SUBQ in 1 to 4 divided doses	• Headache • Fever • Hypersensitivity • Immune suppression • Transaminitis	• CBC with differential • LFTs • Scr
Infliximab	Infliximab 5–10 mg/kg/dose IV for 1 dose	• Infusion-related reaction • Headache • Immune suppression	• Monitor vital signs every 2–10 minutes during infusion • CBC with differential
Aspirin	Aspirin 3–5 mg/kg/dose (up to maximum of 81 mg/dose) PO once daily	• Gastrointestinal ulcers • Hypersensitivity • Renal dysfunction	• Signs or symptoms of bleeding • Renal function
Enoxaparin	**Enoxaparin Prophylaxis** *Aged >2 Months to <18 Years:* • 0.5 mg/kg/dose (up to maximum of 30 mg/dose) SUBQ every 12 hours **Enoxaparin Treatment** *Aged >2 Months to <18 Years:* • 1 mg/kg/dose SUBQ every 12 hours • Monitor antifactor Xa activity (treatment goal: 0.5 to 1).	• Increased risk of bleeding • Thrombocytopenia	• CBC with differential • Renal function

Key: AE = adverse effect; BMP = blood mineral panel; CBC = complete blood count; FDA = Food and Drug Administration; IBW = ideal body weight; IV = intravenous; IVIG = intravenous immunoglobulin; LFT = liver function test; MIS-C = multisystem inflammatory syndrome in children; PO = orally; Scr = serum creatinine; SUBQ = subcutaneously

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Treatment Considerations for Children With MIS-C

Initial Immunomodulatory Therapy for MIS-C

The Panel recommends consultation with a multidisciplinary team when managing immunomodulating therapy for children with MIS-C **(AIII)**. The multidisciplinary team may include experts in cardiology, hematology, infectious disease, intensive care, and rheumatology. MIS-C is defined by multiorgan dysfunction, and input from other pediatric subspecialists may be needed depending on the presentation of the individual patient. Thus, children with MIS-C should be cared for at centers with access to these pediatric specialists.

Intravenous immunoglobulin (IVIG) and glucocorticoids are the most commonly used immunomodulatory medications in reported cohorts of children with MIS-C.[4-12] The American College of Rheumatology has outlined initial diagnostic and treatment considerations in MIS-C and recommends IVIG in combination with glucocorticoids as first-tier therapy for most hospitalized children with MIS-C.[13] Multiple nonrandomized studies suggest that front-line IVIG in combination with glucocorticoids is associated with less treatment failure, faster recovery of cardiac function, shorter intensive care unit (ICU) stay, and decreased requirement for treatment escalation compared to IVIG monotherapy.[5,14-17] Based on these data, the Panel recommends using **IVIG** in combination with low-to-moderate-dose **glucocorticoids** for children hospitalized with MIS-C **(AIIb)**. The Panel recommends against the routine use of IVIG monotherapy for the treatment of MIS-C unless glucocorticoid use is contraindicated **(AIIb)**.

IVIG should be given at a dose of 2 g/kg of ideal body weight up to a maximum dose of 100 grams. The patient's cardiac function and fluid status should be monitored carefully during the IVIG infusion. IVIG can be given in divided doses of 1 g/kg of ideal body weight over 2 days if there is a concern about the patient's fluid status. Methylprednisolone 1 to 2 mg/kg/day, or another glucocorticoid at an equivalent dose, is considered low-to-moderate glucocorticoid dosing. Once there is clinical improvement (i.e., the child is afebrile, end organ dysfunction resolves, and inflammatory markers are trending downward), a steroid taper should be initiated. Typically, the taper lasts for several weeks to avoid rebound inflammation and is guided by the clinical status of the patient.

There remains uncertainty regarding the use of glucocorticoid monotherapy versus IVIG plus glucocorticoids as initial therapy for MIS-C because comparative studies evaluating these 2 treatment approaches have not been conducted. There are limited published data on long-term outcomes in children with MIS-C who were treated with initial glucocorticoid monotherapy. Due to the risk of coronary artery aneurysms in patients with MIS-C, and the proven benefit of IVIG in reducing the frequency of coronary artery aneurysms in patients with Kawasaki disease, many clinicians continue to incorporate IVIG into the treatment regimen for MIS-C.[12,18] Currently, there is insufficient evidence for the Panel to recommend either for or against the use of glucocorticoid monotherapy for MIS-C.

Summary of Published Data on Initial Immunomodulatory Therapy for MIS-C

Intravenous Immunoglobulin in Combination With Glucocorticoids

No randomized clinical trials evaluating IVIG plus glucocorticoids for the treatment of MIS-C have been completed. The comparative benefit of adding steroids to IVIG for MIS-C treatment has been estimated in observational cohorts using statistical techniques to adjust for confounders. The first of these studies employed observation data from a national surveillance system cohort in France and used propensity matching to compare short-term outcomes in children with MIS-C who were treated initially with IVIG (2 gm/kg) alone or IVIG and methylprednisolone (most patients received 1.6–2 mg/kg/day for 5 days).[14] The study team observed a lower risk of treatment failure (defined as persistence of fever 2 days after

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treatment or recurrent fever within 7 days), lesser requirement for hemodynamic support, less severe left ventricular dysfunction, and shorter ICU stays among the children initially treated with the combination therapy.[14] This was a small study, and only 32 patients treated with IVIG and methylprednisolone and 64 patients treated with IVIG alone could be matched based on propensity score.

A larger study in the United States analyzed data from the Overcoming COVID-19 surveillance registry to evaluate immunomodulatory therapy for MIS-C. Initial treatment with IVIG plus glucocorticoids (n = 103) was associated with a lower risk of cardiovascular dysfunction (measured using a composite outcome of left ventricular ejection fraction of <55% or vasopressor use) on or after Day 2 compared to treatment with IVIG alone in an equal number of propensity score-matched patients. The composite outcome occurred in 17% of the patients in the IVIG plus glucocorticoids group versus 31% of the patients in the IVIG alone group (risk ratio 0.56; 95% CI, 0.34–0.94).[15] In addition, patients treated with the combination of IVIG and glucocorticoids were less likely to require adjunctive immunomodulatory therapy than those treated with IVIG alone. Methylprednisolone, the most prescribed glucocorticoid, was administered to 353 patients (68% of the patients, including nonpropensity matched patients, in the entire cohort). Among these patients, the dosing of methylprednisolone ranged from 2 mg/kg/day in 284 patients (80%) to 10 to 30 mg/kg/day in 69 patients (20%).

A third study, the international and pragmatic BATS study, compared patients with MIS-C who received IVIG alone (n = 246) to those who received IVIG and glucocorticoids (n = 208). This study found similar rates for the composite outcome of inotropic support or mechanical ventilation by Day 2 or later or death in both treatment arms. The outcome occurred in 44 of 221 participants (21%) in the IVIG alone arm versus 56 of 180 participants (31%) in the IVIG plus glucocorticoids arm (OR 0.77; 95% CI, 0.33–1.82). However, escalation of immunomodulatory treatment was less common among the patients who received IVIG plus glucocorticoids than among those who received IVIG alone (OR 0.18; 95% CI; 0.10–0.33). This study was notable for including patients with suspected MIS-C (i.e., patients who did not meet CDC or World Health Organization [WHO] criteria for MIS-C) and voluntary reporting of included cases by pediatricians. This multicenter study included sites from 34 counties with potential for more variability in supportive care. In addition, the overall percentage of patients with abnormal cardiac findings (12% of the 538 patients) was lower than in other cohorts.[16]

Intravenous Immunoglobulin Monotherapy

The use of IVIG is long established for Kawasaki disease, a syndrome that has overlapping manifestations with MIS-C, and thus the product's safety profile is well understood. In Kawasaki disease, IVIG prevents the development of coronary artery aneurysms,[18,19] a complication also observed in some patients with MIS-C. IVIG is the most frequently used therapy for MIS-C. In a national survey of U.S. institutional protocols for managing MIS-C, IVIG was the first-line therapy in 98% of 40 participating centers.[20]

Data on the efficacy of IVIG in MIS-C is extrapolated from case series that show mostly favorable outcomes. In a series of 539 MIS-C cases, 77% of the children received IVIG. A sizeable proportion of these children had reduced left ventricular ejection fraction at admission (172 of 503 evaluable patients [34.2%]); the symptom resolved by Day 30 in 156 of the children (90.7%). Although these studies have not described the occurrence of specific adverse events related to IVIG use, the dosing used (IVIG 2 g/kg) has a well-established safety profile when used for Kawasaki disease.[12]

A limitation of all published studies on IVIG use for MIS-C is the frequent and often rapid sequential addition of other immunomodulatory therapies, such as corticosteroids. In addition, there is accumulating evidence that glucocorticoids given in combination with IVIG are more effective as treatment for MIS-C (see discussion above). However, IVIG monotherapy may be a reasonable

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treatment option for a small subset of patients with MIS-C who are stable (i.e., not in shock or with organ-threatening disease) and have contraindications to glucocorticoid therapy. Such contraindications may include concern about the impact on diagnostic evaluation or on the underlying medical condition.

Glucocorticoid Monotherapy

The BATS study described above also evaluated initial treatment with IVIG (n = 246) compared to glucocorticoids (n = 99) and found no differences in primary or secondary outcomes between these 2 cohorts.[16] However, in a subgroup analysis of patients who met the WHO criteria for MIS-C, the glucocorticoid alone group (n = 78) had significantly fewer patients who required respiratory support by Day 2 or later or who died than the IVIG alone group (n = 192).

The BATS study has several limitations. The length of follow-up in this study was not clearly defined, and most outcome measures were evaluated around Day 2 of treatment. Rates of coronary artery aneurysms and myocardial dysfunction and scarring as long-term outcomes were not reported. Further, many patients received additional immunomodulatory agents after Day 1, including 47 patients in the initial glucocorticoids alone group who also received IVIG. This study did not compare initial therapy with glucocorticoids alone versus IVIG in combination with glucocorticoids. Further studies are needed to replicate these findings and to evaluate the long-term outcomes in patients with MIS-C treated with glucocorticoids alone.

Intensification Immunomodulatory Therapy for MIS-C

Children with MIS-C typically respond briskly to immunomodulatory therapy and show clinical improvements within the first 24 hours of treatment. Treatment response is characterized by resolution of fever, improvement of organ function, and reduced levels of inflammatory markers, particularly C-reactive protein. By contrast, refractory disease is often accompanied by persistent fever, worsening organ dysfunction, and increasing levels of inflammatory markers. **Intensification therapy** is recommended for children with refractory MIS-C who do not improve within 24 hours of initial immunomodulatory therapy **(AIII)**. Children with uncontrolled MIS-C despite treatment with IVIG and low-to-moderate-dose glucocorticoids will often continue to deteriorate without further intervention, and this decline in clinical status can be quite rapid.

There are no comparative studies evaluating intensification therapies for MIS-C. Available data on this topic are limited to results from cohort studies in patients with MIS-C, expert opinion, and experience in treating other hyperinflammatory syndromes in children, such as Kawasaki disease and macrophage activation syndrome. For children with refractory MIS-C, the Panel recommends additional immunomodulatory therapy (in alphabetical order) with **anakinra (BIIb)**, higher-dose **glucocorticoids (BIIb)**, or **infliximab (BIIb)**. Currently, there is insufficient evidence to determine which of these agents is most effective for intensification therapy in patients with refractory MIS-C. In certain patients with severe illness, intensification therapy may include dual therapy with higher-dose **glucocorticoids** and **anakinra (BIII)** or higher-dose **glucocorticoids** and **infliximab (BIII)**. Anakinra and infliximab **should not be used** in combination. A second dose of IVIG is not commonly reported in the literature as a strategy for intensification therapy in MIS-C. This may be due to the high rates of IVIG resistance, the rapid pace of disease escalation, and the risk for fluid overload in MIS-C patients.[8] Therefore, the Panel **recommends against** a second dose of **IVIG** for intensification therapy in patients with refractory MIS-C **(BIII)**.

Patients with MIS-C who receive multiple immunomodulatory agents are at risk for infection and need to be monitored carefully. Most children with MIS-C were previously healthy. In patients who have an immune disorder or are taking immunosuppression therapy, the risk of infection is greater. The risks and benefits of treating immunocompromised MIS-C patients with immunomodulatory agents need to be evaluated on a case-by-case basis.

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Summary of Published Data for Intensification Immunomodulatory Therapy for MIS-C

High-Dose Glucocorticoids

High-dose glucocorticoid therapy is defined as methylprednisolone (or an equivalent corticosteroid) dosed at 10 to 30 mg/kg/day given intravenously (IV). Often, this higher dose of glucocorticoids is given for 1 to 3 days with a subsequent return to low-to-moderate dosing (1–2 mg/kg/day). Multiple observational studies have reported the use of high-dose glucocorticoids (methylprednisolone 10–30 mg/kg/day) in children with MIS-C.[15,21-23] In addition, single-center treatment protocols for MIS-C that incorporate high-dose glucocorticoids into the treatment algorithm have been published. Implementation of the protocols has resulted in positive clinical outcomes in patients with MIS-C.[17] There is substantial experience using high-dose glucocorticoids in pediatric patients with other inflammatory conditions, such as Kawasaki disease and macrophage activation syndrome.

Anakinra

Anakinra is the most commonly used biologic medication for the treatment of MIS-C in the United States.[20] Multiple, noncomparative, observational cohorts have reported on the use of anakinra in patients with MIS-C.[8,9,11] This medication has been used extensively with a good safety record in pediatric patients with other hyperinflammatory syndromes (e.g., systemic juvenile idiopathic arthritis, macrophage activation syndrome).[24-26] Anakinra has also been used successfully to treat IVIG-resistant Kawasaki disease. Anakinra has a short half-life (4–6 hours), and the medication can be stopped quickly, which many providers regard as a benefit relative to longer-acting immunomodulators. High-dose anakinra (5–10 mg/kg/day) is recommended for MIS-C based on the improved efficacy of anakinra used at higher doses for macrophage activation syndrome. The duration of anakinra therapy varies in the literature and is used by some patients for long periods (e.g., up to 2 weeks) as a steroid sparing agent.

Infliximab

The Panel recommends a single dose of infliximab 5 to 10 mg/kg IV as an option for intensification therapy. Infliximab has been studied for the treatment of MIS-C in a single-center retrospective study that compared patients treated with IVIG alone (n = 20) to those treated with IVIG and a single dose of infliximab 10 mg/kg IV (n = 52).[27] Of note, infliximab was used as first-line therapy in this study, and the patients were not treated with glucocorticoids. The patients who received IVIG and infliximab were more likely to be admitted to the ICU and had more severe illness than those who received IVIG alone. Yet, the patients who received the combination therapy were less likely to require additional therapy after 24 hours (the primary outcome). In addition, patients who received IVIG and infliximab had shorter admissions to the ICU and less cardiac dysfunction. These results show that infliximab has a therapeutic effect in MIS-C. Infliximab is approved by the Food and Drug Administration for use in children with inflammatory bowel disease and is used widely to treat juvenile idiopathic arthritis. Infliximab has been employed in IVIG-resistant Kawasaki disease.[28,29] Although the half-life of infliximab in MIS-C is unknown, it likely has effects that persist for several weeks. This extended period of drug activity can allow for a steroid-sparing effect in MIS-C.

Antithrombotic Treatment for MIS-C

There is general agreement that patients with MIS-C who do not have risk factors for bleeding should receive low-dose aspirin **(AIII)**. This recommendation is largely due to experience in children with Kawasaki disease and the likelihood of analogous platelet activation and endothelial dysfunction in children with MIS-C.[30] Children treated with aspirin and steroids should also receive gut protection. Patients with MIS-C who have large coronary artery aneurysms (Z-score ≥10) should receive therapeutic anticoagulation according to the American Heart Association guidelines for Kawasaki disease **(AIII)**. Children with left ventricular dysfunction are at risk for intracardiac thrombosis. Patients with MIS-C

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and moderate-to-severe left ventricular dysfunction should receive therapeutic anticoagulation, unless contraindicated due to bleeding risk factors **(AIII)**.

There is less consensus on the use of either prophylactic or therapeutic anticoagulation in patients with MIS-C who do not have large coronary artery aneurysms and/or moderate-to-severe left ventricular dysfunction. Children with MIS-C have marked elevations in D-dimer levels and other abnormalities of coagulation, which suggests that they may be at increased risk for thrombosis.[31] In 1 study of children with acute COVID-19 and MIS-C, indwelling catheters, older age (>12 years), malignancy, admission to the ICU, and elevated D-dimer levels were all independent risk factors for thrombosis.[32] There is less known about the risk of bleeding in children with MIS-C who are treated with anticoagulation. Major bleeding events have been reported in MIS-C patients treated with anticoagulation.[32] Given the uncertainty regarding the benefit of anticoagulation for MIS-C, prophylactic or therapeutic anticoagulation for children with MIS-C who do not have large coronary artery aneurysms or moderate-to-severe left ventricular dysfunction should be considered on a case-by-case basis, taking into account the risk factors for thrombosis.

Antiviral Therapy in MIS-C

The role of antiviral therapy in treating MIS-C has not been systematically studied; however, it is not expected to be beneficial because MIS-C is considered an immune-mediated phenomenon that occurs weeks after a primary SARS-CoV-2 infection. Therefore, the Panel **recommends against** the use of **remdesivir** for patients with MIS-C **(AIII)**.

Critical Care Management

Shock occurs in approximately 50% of patients with MIS-C, and may include elements of distributive, cardiogenic, or hypovolemic shock.[12,33,34] In general, clinicians should manage shock in patients with MIS-C per the usual critical care standards as outlined in the Pediatric Surviving Sepsis Campaign Guidelines.[35]

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Care of Critically Ill Adults With COVID-19

Last Updated: May 31, 2022

Summary Recommendations
Hemodynamics • 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)**. • 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 **(BI)**. • For adults with COVID-19 and shock, the Panel recommends **norepinephrine** as the first-line vasopressor **(AI)**. • For adults with COVID-19 and shock, the Panel recommends titrating vasoactive agents to target a mean arterial pressure (MAP) of 60 to 65 mm Hg over higher MAP targets **(BI)**. • The Panel **recommends against** using **hydroxyethyl starches** for intravascular volume replacement in adult patients with COVID-19 and sepsis or septic shock **(AI)**. • When norepinephrine is available, the Panel **recommends against** using **dopamine** for adult patients with COVID-19 and shock **(AI)**. • As a second-line vasopressor, the Panel recommends adding either **vasopressin** (up to 0.03 units/min) **(BIIa)** or **epinephrine (BIIb)** to norepinephrine to raise MAP to target or adding **vasopressin** (up to 0.03 units/min) **(BIIa)** to decrease norepinephrine dosage. • The Panel **recommends against** using **low-dose dopamine** for renal protection **(AI)**. • The Panel recommends using **dobutamine** in adult patients with COVID-19 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 adult patients with COVID-19 who require vasopressors have an arterial catheter placed as soon as practical, if the resources to do so are available **(BIII)**. • For adult patients with refractory septic shock who have completed a course of corticosteroids to treat 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 starting therapy with high-flow nasal cannula (HFNC) oxygen; if patients fail to respond, noninvasive ventilation (NIV) or intubation and mechanical ventilation should be initiated **(BIIa)**.
• For adults with COVID-19 and acute hypoxemic respiratory failure who do not have an indication for endotracheal intubation and for whom HFNC oxygen is not available, the Panel recommends performing a closely monitored trial of NIV **(BIIa)**.
• For adults with persistent hypoxemia who require HFNC oxygen and for whom endotracheal intubation is not indicated, the Panel recommends a trial of awake prone positioning **(BIIa)**.
• The Panel **recommends against** the use of 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 exposing health care practitioners to SARS-CoV-2 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) **(AI)**.
  • 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)**.

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Summary Recommendations, continued

• 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)**.
  • The Panel recommends using, as needed, intermittent boluses of **neuromuscular blocking agents** (NMBAs) or a 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 the patient's 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)**.
Pharmacologic Interventions
• In the absence of a proven or suspected bacterial infection, the Panel **recommends against** the use of **empiric broad-spectrum antibiotics** in adult patients with severe or critical COVID-19 **(BIII)**.
• As with any hospitalized patient, adult patients with COVID-19 who receive antibiotics should be reassessed daily to minimize the adverse consequences of unnecessary antimicrobial therapy **(AIII)**.
Extracorporeal Membrane Oxygenation
• There is insufficient evidence for the Panel to recommend either for or against the use of extracorporeal membrane oxygenation in adults with COVID-19 and refractory hypoxemia.

Rating of Recommendations: A = Strong; B = Moderate; C = Weak **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 to Critical Care Management of Adults With COVID-19

Last Updated: May 31, 2022

COVID-19 can progress to critical illness, including hypoxemic respiratory failure, acute respiratory distress syndrome (ARDS), septic shock, cardiac dysfunction, thromboembolic disease, hepatic and/or renal dysfunction, central nervous system disease, and exacerbation of underlying comorbidities in both adults and children. In addition, multisystem inflammatory syndrome in adults (MIS-A) can occur several weeks or months after SARS-CoV-2 infection, which can lead to critical illness.

Many of the initial recommendations for the management of critically ill adults with COVID-19 in these Guidelines were extrapolated from experience with other causes of sepsis and respiratory failure.[1] However, there is now a rapidly growing body of evidence regarding the management of critically ill patients with COVID-19.

Treating patients with COVID-19 in the intensive care unit (ICU) often requires managing underlying illnesses or COVID-19-related morbidities. As with any patient who is admitted to the ICU, clinicians also need to focus on preventing ICU-related complications.

Selected Clinical Manifestations of COVID-19 Critical Illness

Inflammatory Response Due to COVID-19 in Adults

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." However, these terms are both imprecise and misnomers, because the magnitude of cytokine elevation in many patients with COVID-19 is modest compared to that in patients with many other critical illnesses, such as sepsis and ARDS.[2,3] In addition, some patients with elevated cytokine levels have no specific pathology that can be attributed to the elevated levels.

Patients with COVID-19 and severe pulmonary involvement often manifest extrapulmonary disease and 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

There are case reports describing patients who had evidence of acute or recent SARS-CoV-2 infection (confirmed by a nucleic acid amplification test [NAAT] or an antigen or antibody test) with minimal respiratory symptoms but with laboratory markers of severe inflammation (e.g., elevated levels of C-reactive protein [CRP], ferritin, D-dimer, cardiac enzymes, liver enzymes, and creatinine) and various other symptoms, including fever and shock. These patients also had signs of cardiovascular, gastrointestinal, dermatologic, and neurologic disease. This constellation of signs and symptoms has been designated MIS-A.[4] To date, most adults with MIS-A have survived. This syndrome is similar to multisystem inflammatory syndrome in children (MIS-C), which is much more well described.

The current case definition for MIS-A from the Centers for Disease Control and Prevention states that patients must be aged ≥21 years, be hospitalized for ≥24 hours or have an illness that results in death, and meet the clinical and laboratory criteria outlined below. The patient should not have a more likely alternative diagnosis for the illness (e.g., bacterial sepsis, exacerbation of a chronic medical condition).

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Clinical Criteria

Patients must have a subjective or documented fever (≥38.0°C) for ≥24 hours prior to hospitalization or within the first 3 days of hospitalization and at least 3 of the following clinical criteria, which must have occurred prior to hospitalization or within the first 3 days of hospitalization. At least 1 must be a primary clinical criterion.

- Primary clinical criteria:
  - Severe cardiac illness. This includes myocarditis; pericarditis; coronary artery dilatation/ aneurysm; or new-onset right or left ventricular dysfunction (left ventricular ejection fraction <50%), second- or third-degree atrioventricular block, or ventricular tachycardia. Cardiac arrest alone does not meet this criterion.
  - Rash **AND** nonpurulent conjunctivitis
- Secondary clinical criteria:
  - New-onset neurologic signs and symptoms. These include encephalopathy in a patient without prior cognitive impairment, seizures, meningeal signs, or peripheral neuropathy (including Guillain-Barré syndrome).
  - Shock or hypotension that are not attributable to medical therapy (e.g., sedation, renal replacement therapy)
  - Abdominal pain, vomiting, or diarrhea
  - Thrombocytopenia (platelet count <150,000 cells/µL)

Laboratory Criteria

- The presence of laboratory evidence of inflammation **AND** SARS-CoV-2 infection
- Elevated levels of at least 2 of the following:
  - CRP
  - Ferritin
  - Interleukin (IL)-6
  - Erythrocyte sedimentation rate
  - Procalcitonin
- A positive SARS-CoV-2 test result for current or recent infection using a reverse transcription polymerase chain reaction, serology, or antigen test

These criteria must be met by the end of Day 3 of hospitalization, where the date of hospital admission is Day 0.

Because there is no specific diagnostic test for MIS-A, diagnosis of this inflammatory syndrome is one of exclusion after other causes (e.g., bacterial sepsis) 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-1 receptor antagonist therapy.[5-7]

COVID-19-Induced Cardiac Dysfunction, Including Myocarditis

The published literature describes cardiac injury or dysfunction in up to 24% of adults who are hospitalized with COVID-19.[8] COVID-19 may be associated with an array of cardiovascular complications, including acute coronary syndrome, myocarditis, stress (Takotsubo) cardiomyopathy,

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arrythmias, and thromboembolic disease.[9]

Thromboembolic Events and COVID-19

Critically ill adults with COVID-19 have been observed to have a prothrombotic state and higher rates of venous thromboembolic disease. In some studies, thromboemboli have been diagnosed even in patients who received chemical prophylaxis with heparinoids.[10-12] Autopsy studies provide additional evidence of both thromboembolic disease and microvascular thrombosis in patients with COVID-19.[13] Some authors have called for routine surveillance of ICU patients for venous thromboembolism.[14] See Antithrombotic Therapy in Patients With COVID-19 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 adults with severe COVID-19.[15] In a 2020 multicenter cohort study of critically ill adults in the United States, 20.6% of patients developed acute kidney injury (AKI) that was treated with renal replacement therapy (RRT).[16] In a cohort of critically ill adults in Brazil, the development of an AKI that required RRT was associated with poor prognosis.[17]

Other Intensive Care Unit-Related Complications

When treating patients with COVID-19, clinicians also need to minimize the risk of conventional ICU complications. Patients who are critically ill with COVID-19 are at risk for nosocomial infections, such as ventilator-associated pneumonia, hospital-acquired pneumonia, catheter-related bloodstream infections, and other complications of critical illness care.

Critically ill patients with COVID-19 may also experience prolonged delirium and/or encephalopathy. The risk factors that are associated with delirium include the use of mechanical ventilation, restraints, benzodiazepines, opioids, vasopressors, and antipsychotics.[18,19] Neurological manifestations of COVID-19 have been described in a significant proportion of hospitalized patients and are more frequent in patients with severe disease.[20] Autopsy studies have reported both macrovascular and microvascular thrombosis with evidence of hypoxic ischemia.[21] Adequate management of critically ill patients with COVID-19 includes paying careful attention to best sedation practices and monitoring for stroke.

Important Considerations in the Care of Critically Ill Patients With COVID-19

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 that are used off-label to treat COVID-19 and concurrent drugs should be considered.

Sedation Management in Adults With COVID-19

International guidelines provide recommendations on the prevention, detection, and treatment of pain, sedation, and delirium in ICU patients.[22,23] 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.[24,25]

The Society of Critical Care Medicine's (SCCM) 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;

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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.[26] 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.[27] Despite the known benefits of the A-F Bundle, its impact has not been directly assessed in patients with COVID-19; however, 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 SCCM's PADIS guidelines. This puts patients at additional risk for ICU and post-ICU complications.

Post-Intensive Care Syndrome

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.[28] 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.[29-31] Cognitive dysfunction affects 30% to 80% of patients discharged from the ICU.[32-34] About 50% of ICU survivors do not return to work within 1 year after discharge.[35] 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 1 study, a third of family members who had major decision-making roles experienced mental health problems, such as depression, anxiety, and PTSD.[36]

Some patients with COVID-19 who have been treated in the ICU express manifestations of PICS.[37] 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.

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 on 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

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decision makers, support frontline clinicians, and provide direct patient care services when needed.

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

Acknowledgments

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Hemodynamics for Adults

Last Updated: July 8, 2021

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, adult patients with COVID-19 who require fluid resuscitation or hemodynamic management of shock should be treated and managed identically to adult patients with septic shock.[1]

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

In a systematic review and meta-analysis of 13 randomized clinical trials in intensive care unit (ICU) patients without COVID-19 (n = 1,652),[2] dynamic assessment to guide fluid therapy reduced mortality (risk ratio 0.59; 95% CI, 0.42–0.83), 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 greatest accuracy.[3] The static parameters included components of early goal-directed therapy (e.g., central venous pressure, mean arterial pressure [MAP]).

Resuscitation of patients with shock who do not have COVID-19 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 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 compared the use of balanced and unbalanced crystalloids for intravenous (IV) fluid administration in critically ill adults without COVID-19 (n = 15,802). The rate of the composite outcome of death, new renal-replacement therapy, or persistent renal dysfunction was lower in the balanced crystalloids group than in the unbalanced 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). Compared to treatment with unbalanced crystalloids, treatment with balanced crystalloids resulted in fewer deaths (aOR 0.74; 95% CI, 0.59–0.93; $P = 0.01$) and more vasopressor-free and renal replacement-free days.[6] A subsequent meta-analysis of 21 non-COVID-19 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. The trial reported nonsignificant differences between the treatment groups in hospital mortality (OR 0.91; 95% CI, 0.83–1.01) and acute kidney injury (OR

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0.92; 95% CI, 0.84–1.00).[7]

Recommendation

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

Rationale

A meta-analysis of 20 non-COVID-19 randomized controlled trials (n = 13,047) that compared the use of albumin or fresh-frozen plasma to crystalloids in critically ill patients found no difference in all-cause mortality between the treatment groups.[8] In contrast, 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 among the patients who received albumin (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 **(BI)**.

Recommendation

- For adults with COVID-19 and shock, the Panel recommends **norepinephrine** as the first-choice vasopressor **(AI)**.

Rationale

Norepinephrine increases MAP due to its vasoconstrictive effects, with little change in heart rate and less increase in stroke volume compared to dopamine. Dopamine increases MAP and cardiac output, primarily due to an increase in stroke volume and heart rate. Norepinephrine is more potent than dopamine and may be more effective at reversing hypotension in patients with septic shock. Dopamine may be particularly useful in patients with compromised systolic function, but it causes more tachycardia and may be more arrhythmogenic than norepinephrine.[10] It may also influence the endocrine response via the hypothalamic pituitary axis and have immunosuppressive effects.[11] A systematic review and meta-analysis of 11, non-COVID-19 randomized controlled trials that compared vasopressors used to treat patients with septic shock found that norepinephrine use resulted in lower all-cause mortality (RR 0.89; 95% CI, 0.81–0.98) and a lower risk of arrhythmias (RR 0.48; 95% CI, 0.40–0.58) than dopamine use.[12] Although the beta-1 activity of dopamine would be useful in patients with myocardial dysfunction, the greater risk of arrhythmias limits its use.[13,14]

Recommendation

- For adults with COVID-19 and shock, the Panel recommends titrating vasoactive agents to target a MAP of 60 to 65 mm Hg, over higher MAP targets **(BI)**.

Rationale

A recent individual patient-data meta-analysis of two, non-COVID-19 randomized controlled trials (n = 894) comparing higher versus lower blood pressure targets for vasopressor therapy in adult patients with shock reported no significant difference between the patients in the higher and lower target groups in 28-day mortality (OR 1.15; 95% CI, 0.87–1.52), 90-day mortality (OR 1.08; 95% CI, 0.84–1.44), myocardial injury (OR 1.47; 95% CI, 0.64–3.56), or limb ischemia (OR 0.92; 95% CI, 0.36–2.10).[15] The risk of arrhythmias was increased in patients allocated to the higher target group (OR 2.50; 95% CI, 1.35–4.77). Similarly, the recently published "65 Trial," a randomized clinical trial in patients without COVID-19 (n = 2,463), reported no significant difference in mortality between patients with

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vasopressor therapy guided by a MAP target of 60 to 65 mm Hg and those with treatment guided by a higher, standard of care MAP target (41% vs. 43.8%; RR 0.93; 95% CI, 0.85–1.03).[16] With an indication of improved outcome with lower MAP targets (and no firm indication of harm), the Panel recommends titrating vasoactive agents to a MAP target of 60 to 65 mm Hg **(BI)**.

Additional Recommendations for Adults With COVID-19 and Shock Based on General Principles of Critical Care

- The Panel **recommends against** using hydroxyethyl starches for intravascular volume replacement in adult patients with COVID-19 and sepsis or septic shock **(AI)**.
- When norepinephrine is available, the Panel **recommends against** using **dopamine** for adult patients with COVID-19 and shock **(AI)**.
- As a second line vasopressor, the Panel recommends adding either **vasopressin** (up to 0.03 units/min) **(BIIa)** or **epinephrine (BIIb)** to norepinephrine to raise MAP to target or adding vasopressin (up to 0.03 units/min) **(BIIa)** to decrease norepinephrine dosage.
- The Panel **recommends against** using **low-dose dopamine** for renal protection **(AI)**.
- The Panel recommends using **dobutamine** in adult patients with COVID-19 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 adult patients with COVID-19 who require vasopressors have an arterial catheter placed as soon as practical, if resources are available **(BIII)**.
- For adult patients with refractory septic shock who have completed a course of corticosteroids to treat 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 hydrocortisone 200 mg IV per day administered either as an infusion or in intermittent doses. The duration of hydrocortisone therapy is usually a clinical decision.
  - Adult 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 for Adults

Last Updated: May 31, 2022

The COVID-19 Treatment Guidelines Panel's (the Panel) recommendations in this section were informed by the recommendations in the Surviving Sepsis Campaign Guidelines for managing sepsis and COVID-19 in adults.

Severe illness in people with 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 who are receiving supplemental oxygen is unknown. However, a target SpO_2 of 92% to 96% seems logical, considering that indirect evidence from patients without COVID-19 suggests that an SpO_2 of <92% or >96% may be harmful.

The potential harm of maintaining an SpO_2 of <92% was demonstrated during a trial that randomly assigned patients with ARDS who did not have COVID-19 to either a conservative oxygen strategy (target SpO_2 of 88% to 92%) or a liberal oxygen strategy (target SpO_2 of ≥96%). The trial was stopped early due to futility after enrolling 205 patients, but increased mortality was observed at Day 90 in the conservative oxygen strategy arm (between-group risk difference of 14%; 95% CI, 0.7% to 27%) and a trend toward increased mortality was observed at Day 28 (between-group risk difference of 8%; 95% CI, -5% to 21%).[1]

The results of a meta-analysis of 25 randomized trials that involved patients without COVID-19 demonstrate the potential harm of maintaining an SpO_2 of >96%. This study found that a liberal oxygen supplementation strategy (median fraction of inspired oxygen [FiO_2] of 0.52) was associated with an increased risk of in-hospital mortality (relative risk 1.21; 95% CI, 1.03–1.43) when compared to a more conservative SpO_2 supplementation strategy (median FiO_2 of 0.21).[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 using high-flow nasal canula (HFNC) oxygen, noninvasive ventilation (NIV), intubation and mechanical ventilation, or extracorporeal membrane oxygenation. In this section, mechanical ventilation refers to the delivery of positive pressure ventilation through an endotracheal or tracheostomy tube. NIV refers to the delivery of either continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) through a noninvasive interface, such as a face mask or nasal mask.

Nonmechanically Ventilated Adults With Acute Hypoxemic Respiratory Failure

High-Flow Nasal Cannula Oxygen and Noninvasive Ventilation

Recommendations

- For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy, the Panel recommends starting therapy with HFNC oxygen; if patients fail to respond, NIV or intubation and mechanical ventilation should be initiated **(BIIa)**.
- For adults with COVID-19 and acute hypoxemic respiratory failure who do not have an indication

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for endotracheal intubation and for whom HFNC oxygen is not available, the Panel recommends performing a closely monitored trial of NIV **(BIIa)**.

Rationale

HFNC oxygen is preferred over NIV in patients with acute hypoxemic respiratory failure. As there are no studies that directly compare the use of HFNC oxygen and NIV delivered by a mask in patients with COVID-19, this guidance is based on data from an unblinded clinical trial in patients without COVID-19 who had acute hypoxemic respiratory failure. Study participants were randomized to receive HFNC oxygen, conventional oxygen therapy, or NIV. The patients in the HFNC oxygen arm had more ventilator-free days (mean of 24 days) than those in the conventional oxygen therapy arm (mean of 22 days) or the NIV arm (mean of 19 days; $P = 0.02$). In addition, 90-day mortality was higher in both the conventional oxygen therapy arm (HR 2.01; 95% CI, 1.01–3.99) and the NIV arm (HR 2.50; 95% CI, 1.31–4.78) than in the HFNC oxygen arm. In the subgroup of severely hypoxemic patients (those with a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen [PaO_2/FiO_2] ≤200 mm Hg), the intubation rate was lower in the HFNC oxygen arm than in the conventional oxygen therapy arm or the NIV arm (HR 2.07 and 2.57, respectively).[3]

The trial's findings were corroborated by a meta-analysis of 8 trials with 1,084 participants that assessed the effectiveness of oxygenation strategies. Compared to NIV, HFNC oxygen reduced the rate of intubation (OR 0.48; 95% CI, 0.31–0.73) and intensive care unit (ICU) mortality (OR 0.36; 95% CI, 0.20–0.63).[4]

One small study compared the use of NIV delivered by a helmet device to HFNC oxygen in patients with COVID-19. The HENIVOT trial randomized 109 patients with moderate or severe COVID-19 (defined as those who had PaO_2/FiO_2 <200 mm Hg) to receive either NIV via a helmet device or HFNC oxygen. The study found no difference between the arms in the primary outcome of respiratory support-free days. However, only 30% of the patients in the NIV arm required endotracheal intubation compared to 51% of patients in the HFNC oxygen arm ($P = 0.03$).[5]

Two larger studies have compared NIV with conventional oxygen therapy. The RECOVERY-RS trial was an adaptive randomized controlled trial that was essentially conducted as 2 separate trials that compared NIV and HFNC oxygen to the same conventional oxygen therapy control group.[6] The trial was stopped early and enrolled fewer than a third of the planned sample size of 4,002 participants. Between April 2020 and May 2021, 1,273 adults with COVID-19-related acute hypoxemic respiratory failure were randomized to receive NIV (n = 380), HFNC oxygen (n = 418), or conventional oxygen therapy (n = 475). The primary endpoint was a composite of endotracheal intubation or death within 30 days. The proportion of patients who met the primary endpoint was significantly lower in the NIV arm compared to the conventional oxygen therapy arm (36.3% vs. 44.4%; $P = 0.03$), and this difference was entirely due to a reduction in the number of patients who required intubation and not due to mortality. There was no significant difference between the HFNC oxygen arm and the conventional oxygen therapy arm in the occurrence of the primary endpoint (44.3% vs. 45.1%; $P = 0.83$).

There was substantial crossover between the groups, but an inverse probability weighting analysis that corrected for the bias that this may have introduced did not change the results. Adverse events were more common in the NIV arm. Initially, a comparison between NIV and HFNC oxygen was not planned, but a post hoc analysis found that the proportion of patients who required endotracheal intubation or who died was lower in the NIV arm than in the HFNC oxygen arm (34.6% vs. 44.3%; $P = 0.02$).

In contrast to the RECOVERY-RS trial, the HiFlo-COVID trial randomized 220 patients to receive HFNC oxygen or conventional oxygen therapy and found that a smaller proportion of patients in the HFNC oxygen arm required intubation (34.3% vs. 51.0%; $P = 0.03$). Patients in the HFNC arm also had a shorter median time to recovery (11 vs. 14 days; $P = 0.047$).[7]

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The conflicting results of these studies make it difficult to draw inferences from the data. Additionally, the RECOVERY-RS trial was stopped long before it reached its planned sample size for reasons that were not related to futility, efficacy, or harm, and inferring benefit in this context is questionable. Furthermore, the Panel recognizes that in patients who need more oxygen support than a conventional nasal cannula can provide, most clinicians will administer oxygen via a HFNC and subsequently progress to NIV if needed. Therefore, the pertinent clinical question is whether HFNC oxygen or NIV should be used in situations where a patient fails to respond to conventional oxygen therapy. Other than the post hoc analysis in the RECOVERY-RS trial, no study has specifically investigated this question.

NIV is an aerosol-generating procedure, and it may increase the risk of nosocomial transmission of SARS-CoV-2.[8,9] It remains unclear whether the use of HFNC oxygen results in a lower risk of nosocomial SARS-CoV-2 transmission than NIV.

Awake Prone Positioning in Nonmechanically Ventilated Adults

Recommendations

- For adults with persistent hypoxemia who require HFNC oxygen and for whom endotracheal intubation is not indicated, the Panel recommends a trial of awake prone positioning **(BIIa)**.
- The Panel **recommends against** the use of 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)**.

Additional Considerations

- Patients who can adjust their position independently and tolerate lying prone can be considered for awake prone positioning.
- 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.[10]
- Some patients do not tolerate awake prone positioning. Failure rates as high as 63% have been reported in the literature.[11]
- Awake prone positioning **should not be used** as a substitute for intubation and mechanical ventilation in patients with refractory hypoxemia who otherwise meet the indications for these interventions.
- Awake prone positioning may be infeasible or impractical in patients with:
  - Spinal instability
  - Facial or pelvic fractures
  - An open chest or unstable chest wall
- Awake prone positioning should be used with caution in patients with confusion, delirium, or hemodynamic instability and in patients who cannot independently change position or who have had recent abdominal surgery, nausea, or vomiting.

Rationale

Awake prone positioning, or having a nonintubated patient lie on their stomach, may improve oxygenation and prevent the patient from progressing to requiring intubation and mechanical ventilation. Although prone positioning has been shown to improve oxygenation and outcomes in patients with moderate to severe ARDS who are receiving mechanical ventilation,[12,13] there is less evidence regarding the benefit of prone positioning in awake patients who require supplemental oxygen without mechanical ventilation. Several case series of patients with COVID-19 who required oxygen or NIV have reported

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that awake prone positioning improves oxygenation,[14-17] and some series have also reported low intubation rates after awake prone positioning.[14,16]

The Awake Prone Positioning Meta-Trial Group conducted the largest trial to date on awake prone positioning. This was a prospective, multinational meta-trial of 6 open-label, randomized, controlled, superiority trials that compared awake prone positioning to standard care in adults who required HFNC oxygen for acute hypoxemic respiratory failure due to COVID-19.

The study enrolled 1,126 patients between April 2, 2020, and January 26, 2021, and the intention-to-treat analysis included 1,121 patients. Of the 564 patients who underwent awake prone positioning, 223 (40%) met the primary composite endpoint of intubation or death within 28 days of enrollment; among the 557 patients who received standard care, 257 (46%) met the primary endpoint (relative risk 0.86; 95% CI, 0.75−0.98). Regarding the individual components of the composite endpoint, the incidence of intubation by Day 28 was lower in the awake prone positioning arm than in the standard care arm (HR for intubation 0.75; 95% CI, 0.62−0.91). There was no difference in 28-day mortality between the awake prone positioning arm and the standard care arm (HR for mortality 0.87; 95% CI, 0.68−1.11). During the first 14 days of the study, the median daily duration of awake prone positioning was 5.0 hours (IQR 1.6–8.8 hours). However, the median daily duration varied from 1.6 hours to 8.6 hours across the individual trials. Longer daily durations for awake prone positioning were associated with treatment success by Day 28. This study evaluated the incidences of certain adverse events, including skin breakdown, vomiting, and central or arterial line dislodgement. These events occurred infrequently during the study, and the incidences for these events were similar between the arms. No cardiac arrests occurred during awake prone positioning.[18]

Though the optimal daily duration of awake prone positioning is unclear, only 25 of 151 patients (17%) who had an average of ≥8 hours of awake prone positioning per day met the primary endpoint of intubation or death in the Awake Prone Positioning Meta-Trial, compared with 198 of 413 patients (48%) who remained in awake prone positioning for <8 hours per day. This is consistent with past clinical trials of prone positioning in mechanically ventilated patients with ARDS, during which clinical benefits were observed with longer durations of prone positioning.[12,13]

Intubation for Mechanical Ventilation

Recommendation

- If intubation becomes necessary, the procedure should be performed by an experienced practitioner in a controlled setting due to the enhanced risk of exposing health care practitioners to SARS-CoV-2 during intubation **(AIII)**.

Rationale

It is essential to closely monitor hypoxemic patients with COVID-19 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

General Considerations

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

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weight) over higher VT ventilation (VT >8 mL/kg) **(AI)**.

- 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 ARDS

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 3 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 levels of PEEP in those with moderate (PaO_2/FiO_2 100–200 mm Hg) and severe ARDS (PaO_2/FiO_2 <100 mm Hg).[19]

Although there is no clear standard as to what constitutes a high level of PEEP, a conventional threshold is >10 cm H_2O.[20] 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. In these patients, higher PEEP levels may cause harm by compromising hemodynamics and cardiovascular performance.[21,22] Other studies have reported that patients with moderate to severe ARDS due to COVID-19 had low lung compliance, similar to the lung compliance seen in patients with conventional ARDS.[23-26] These seemingly contradictory observations suggest that COVID-19 patients with ARDS are a heterogeneous population, and assessments for responsiveness to higher levels of PEEP should be individualized based on oxygenation and lung compliance. Clinicians should monitor patients for known side effects of higher levels of PEEP, such as barotrauma and hypotension.

In the prepandemic PROSEVA study of patients with moderate or severe early ARDS (PaO_2/FiO_2 <150 mm Hg) who required mechanical ventilation, the patients who were randomized to undergo prone positioning for ≥16 hours per day had improved survival compared to those who remained in the supine position throughout their course of mechanical ventilation.[12] A meta-analysis evaluated the results of the PROSEVA study and 7 other randomized controlled trials that investigated the use of prone positioning in people with ARDS. The subgroup analysis revealed that patients who remained prone for ≥12 hours per day had a lower mortality rate than those who remained in the supine position (risk ratio 0.74; 95% CI, 0.56–0.99). Prone positioning improved oxygenation in all of the trials; patients in the prone positioning arms had higher PaO_2/FiO_2 on Day 4 than those in the supine positioning arms (mean difference of 23.5 mm Hg; 95% CI, 12.4–34.5).[27]

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The use of prone positioning may be associated with serious adverse events, including unplanned extubation or central catheter removal; however, the meta-analysis found no differences in the frequencies of these events between the prone positioning and supine positioning arms. The use of prone positioning was associated with an increase in the frequency of pressure sores (risk ratio 1.22; 95% CI, 1.06–1.41) and endotracheal tube obstruction (risk ratio 1.76; 95% CI, 1.24–2.50) in the 3 studies that evaluated these complications.

Neuromuscular Blockade in Mechanically Ventilated Adults With Moderate to Severe ARDS

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** (NMBAs) or a 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 the patient's anxiety and pain can be adequately monitored and controlled **(BIII)**.

Rationale

The recommendation for intermittent boluses of NMBAs or a continuous infusion of NMBAs 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 ARDS

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** the use of 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

A recruitment maneuver refers to a temporary increase in airway pressure during mechanical ventilation to open collapsed alveoli and improve oxygenation. No studies have assessed the effect of recruitment maneuvers on oxygenation in patients with severe ARDS due to COVID-19. However, a systematic review and meta-analysis of 6 trials of recruitment maneuvers in patients with ARDS who did not have COVID-19 found that recruitment maneuvers reduced mortality, improved oxygenation 24 hours after the maneuver, and decreased the need for rescue therapy.[28] 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 8 randomized controlled trials in patients without COVID-19 (n = 2,544) that found that recruitment maneuvers did not reduce hospital mortality (risk ratio 0.90; 95% CI, 0.78–1.04). However, a subgroup

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analysis found that traditional recruitment maneuvers significantly reduced hospital mortality (risk ratio 0.85; 95% CI, 0.75–0.97). Mortality was higher among patients who were treated with incremental PEEP titration recruitment maneuvers than among those who were treated with traditional recruitment maneuvers, but this difference was not statistically significant (risk ratio 1.06; 95% CI, 0.97–1.17).[20]

Although there are no published studies on the use of inhaled nitric oxide in patients with COVID-19, a Cochrane review of 13 trials that evaluated the use of inhaled nitric oxide in patients with ARDS found no mortality benefit.[29] Because the review showed a transient benefit for oxygenation, it is reasonable to attempt using inhaled nitric oxide as a rescue therapy in patients with COVID-19 and severe ARDS after other options have failed. However, if the use of nitric oxide does not improve a patient's oxygenation, it should be tapered quickly to avoid rebound pulmonary vasoconstriction, which may occur when nitric oxide is discontinued after prolonged use.

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Pharmacologic Interventions for Critically Ill Patients

Last Updated: May 31, 2022

Empiric Broad-Spectrum Antibiotic Therapy

Recommendations

- In the absence of a proven or suspected bacterial infection, the COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of **empiric broad-spectrum antibiotics** in patients with severe or critical COVID-19 **(BIII)**.
- As with any hospitalized patient, patients with COVID-19 who receive antibiotics should be reassessed daily to minimize the adverse consequences of unnecessary antimicrobial therapy **(AIII)**.

Rationale

Variable rates of community- and hospital-acquired infections have been reported in adult patients with COVID-19. Bacterial coinfection at the time of hospitalization has been reported in 1% to 3.5% of patients with COVID-19.[1,2] Secondary infections have been reported in 14% to 37% of intensive care unit patients, but the reported rates have been influenced by differences in the severity of illness, duration of hospitalization, method of diagnosis, and time period studied.[3,4]

There are no clinical trials that have evaluated the use of empiric broad-spectrum antibiotics in patients with severe or critical COVID-19 or other coronavirus infections. Routine, empiric use of antibiotics in patients with severe or critical COVID-19 **is not recommended (BIII)**; this recommendation is intended to mitigate the unintended consequences of side effects and resistance. The use of antibiotics may be considered in 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.

The use of antibiotics in patients with severe or critical COVID-19 should follow guidelines established for other hospitalized patients (i.e., for hospital-acquired pneumonia, ventilator-associated pneumonia, or central line-associated bloodstream infection). It is unclear whether using the corticosteroids or other immunomodulatory agents that are recommended in the Guidelines should alter such approaches.

Therapeutic Management of Hospitalized Adults With COVID-19

See Therapeutic Management of Hospitalized Adults With COVID-19 for the Panel's recommendations on when to use baricitinib, dexamethasone, remdesivir, and tocilizumab.

Immune-Based Therapy

See the Immunomodulators section for recommendations on the use of immunomodulators.

Adjunctive Therapy

Recommendations regarding the use of adjunctive therapies in critical care settings, including antithrombotic therapy and vitamin C, can be found in Antithrombotic Therapy in Patients With COVID-19, Therapeutic Management of Hospitalized Adults With COVID-19, and Vitamin C.

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Extracorporeal Membrane Oxygenation for Adults

Last Updated: May 31, 2022

Recommendation

- There is insufficient evidence for the COVID-19 Treatment Guidelines Panel to recommend either for or against the use of extracorporeal membrane oxygenation (ECMO) in adults 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] Several multicenter, observational cohort studies from the first half of 2020[8-10] reported that patients who required ECMO for COVID-19 had a similar mortality to patients in a 2018 randomized study who did not have COVID-19 but who had ARDS and received ECMO.[3]

However, a recent analysis reported worse outcomes over time among patients who required ECMO for COVID-19.[11] The analysis used data from 4,812 patients in the international Extracorporeal Life Support Organization (ELSO) Registry who had COVID-19 and who received ECMO in 2020. At centers that provided ECMO throughout 2020, patients who started ECMO before May 1, 2020, had a 90-day mortality of 36.9% after ECMO initiation (95% CI, 34.1% to 39.7%). At the same centers, patients who initiated ECMO between May 2 and December 31, 2020, had a 90-day mortality of 51.9% (95% CI, 50.0% to 53.8%). Furthermore, at centers that started using ECMO for patients with COVID-19 after May 1, 2020, the 90-day mortality after ECMO initiation was 58.9% (95% CI, 55.4% to 62.3%). These observational data should be interpreted with caution, as they may reflect a changing case mix of patients with COVID-19 who were referred for ECMO.

Without data from controlled trials that have evaluated 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.

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. More information on the use of ECMO in patients with COVID-19 can be found on ELSO's Extracorporeal Membrane Oxygenation in COVID-19 website and ClinicalTrials.gov.

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Introduction to Critical Care Management of Children With COVID-19

Last Updated: May 31, 2022

COVID-19 may lead to critical illness in children, including hypoxemic respiratory failure, acute respiratory distress syndrome (ARDS), septic shock, cardiac dysfunction, thromboembolic disease, hepatic or renal dysfunction, central nervous system disease, and exacerbation of underlying comorbidities. In addition, multisystem inflammatory syndrome in children (MIS-C) is a rare, postinfectious complication of SARS-CoV-2 and is frequently associated with critical illness.

Data informing the optimal management of children with acute COVID-19 or MIS-C are limited. In general, management should follow the principles of pediatric critical care usually applied to non-COVID-19-related illness, such as the Pediatric Acute Lung Injury Consensus Conference (PALICC) recommendations and the *Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children*. For patients with COVID-19 in the intensive care unit (ICU), treatment often requires managing underlying illnesses other than COVID-19 that may have contributed to the need for ICU admission, as well as managing COVID-19 complications. Finally, prevention of ICU-related complications is critical to achieving optimal clinical outcomes for any patient admitted to the ICU.

Selected Clinical Manifestations of COVID-19 Critical Illness

Inflammatory Response

Patients with COVID-19 may develop a hyperinflammatory state, which appears to be distinct from classic "cytokine storm" syndromes (e.g., macrophage activation syndrome in juvenile idiopathic arthritis, familial hemophagocytic lymphohistiocytosis). This phenomenon is less well-described in children than in adults.

Multisystem Inflammatory Syndrome in Children

MIS-C is a rare, postinfectious complication of SARS-CoV-2 that is characterized by persistent fever, systemic inflammation, and multisystem organ dysfunction. The majority of children with MIS-C require ICU-level care, primarily for shock and for vasopressor and inotropic support.[1-3] For details on the definition of MIS-C, clinical features, and recommended treatments, see Special Considerations in Children and Therapeutic Management of Hospitalized Pediatric Patients With Multisystem Inflammatory Syndrome in Children (MIS-C) (With Discussion on Multisystem Inflammatory Syndrome in Adults [MIS-A]).

Cardiac Dysfunction, Including Myocarditis

Although cardiac involvement is common in patients with MIS-C,[2,4] cardiac manifestations have rarely been described in children with acute COVID-19. Myocarditis, cardiac conduction abnormalities, and coronary artery aneurysms have been reported in patients with MIS-C. Myocarditis may also occur after SARS-CoV-2 vaccination, particularly in adolescent males, although the clinical course generally is relatively mild.[5]

Thromboembolic Events

Limited data characterize the prevalence of thromboembolic disease in children with COVID-19 or MIS-C. In a multicenter, retrospective cohort study including 814 hospitalized patients with COVID-19

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or MIS-C, thromboembolic events were detected in 2.1% of patients with COVID-19 and 6.5% of patients with MIS-C.[6] The same study conducted a multivariable analysis and found that the following variables were associated with increased risk of thromboembolic events: children aged ≥12 years, MIS-C, central venous catheters, and underlying malignancies. See Antithrombotic Therapy in Patients With COVID-19 for additional recommendations.

Acute Kidney Injury

Acute kidney injury is estimated to occur in 12% to 44% of hospitalized children with COVID-19 or MIS-C, but the need for renal replacement therapy is extremely rare.[7-10]

Neurologic Involvement

Neurologic involvement is common in children with COVID-19 or MIS-C and is estimated to occur in approximately 30% to 40% of children hospitalized with these conditions.[2,11] Severe neurologic manifestations, including severe encephalopathy, stroke, demyelinating conditions, cerebral edema, and Guillain-Barré syndrome, have also been described.[11]

Important Considerations in the Care of Critically Ill Patients With COVID-19

Considerations for the care of children with COVID-19 or MIS-C should generally follow the usual principles of pediatric critical care. Sedation management and considerations related to post-intensive care syndrome–pediatric (PICS-p) are discussed below. See Oxygenation and Ventilation for Children, Hemodynamic Considerations for Children, and Extracorporeal Membrane Oxygenation for Children for more information on pediatric critical care.

Sedation Management

Guidelines for the management of pain, agitation, neuromuscular blockade, delirium, and early mobility (PANDEM) in infants and children admitted to the pediatric ICU have recently been published.[12] In general, children with COVID-19 or MIS-C who require mechanical ventilation should be managed per the usual critical care for patients with respiratory failure who require mechanical ventilation. The usual care includes sedation with the minimal effective dose required to tolerate mechanical ventilation, optimize gas exchange, and minimize the risk of ventilator-induced lung injury. Using validated pain and sedation scales, the critical care team should set a sedation/pain target based on the phase of ventilation.

Two large randomized controlled trials examined the use of protocols to manage sedation titration in children receiving mechanical ventilation.[13,14] In both studies, participants received usual care or protocol-driven care implemented by nurses. The studies found that the use of the protocols did not demonstrate a significant benefit on outcomes, such as the duration of ventilation. However, a patient's risk of harm from protocolized sedation is generally low, which led the Society of Critical Care Medicine to issue a conditional recommendation, based on low-level evidence, in its PANDEM clinical practice guidelines suggesting the use of protocolized sedation in children who are critically ill and receiving mechanical ventilation.[12]

Studies evaluating data on the effect of early mobility protocols on critically ill children are limited. One trial evaluated the safety and feasibility of early mobilization in 58 patients who were randomized to receive usual care or early physical therapy, occupational therapy, and speech therapy consultation within 72 hours of admission to the pediatric ICU.[15] Although no differences between the arms were demonstrated for clinical, functional, or quality of life outcomes, the study found that the early rehabilitation consultations were safe and feasible.

Ongoing trials are measuring the effect of early mobilization on patient-centered outcomes in children

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receiving mechanical ventilation. The PANDEM guideline statement issued by the Society of Critical Care Medicine conditionally recommends, based on a low quality of evidence, implementing early mobilization strategies in children when feasible, which likely would apply to children with COVID-19 or MIS-C.[12]

Post-Intensive Care Syndrome

In recent years, there has been a growing awareness that PICS can occur in pediatric patients. PICS-p has been demonstrated to have a multifaceted effect on the physical, cognitive, emotional, and social health of child survivors of critical illness and their families.[16] Furthermore, many pediatric survivors of sepsis or ARDS manifest significant impairments in physical, cognitive, and emotional health.[17-19] Although no clear data characterize the prevalence of PICS-p or long-term morbidity in children with COVID-19 or MIS-C, the prevalence is expected to be similar to that observed in other populations with similar illness severities.

Acknowledgments

For these pediatric recommendations, the COVID-19 Treatment Guidelines Panel integrated the recommendations from pediatric-specific guidelines, including the European Society of Paediatric and Neonatal Intensive Care's recommendations[20] for the care of critically ill children with COVID-19 and the Surviving Sepsis Campaign's perspective on managing sepsis in children with COVID-19.[21] In addition, recommendations from several non-COVID-19-specific treatment guidelines, such as the *Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children*,[22] the PALICC recommendations,[23] and the Society of Critical Care Medicine's PANDEM guidelines,[12] were integrated.

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Hemodynamic Considerations for Children

Last Updated: May 31, 2022

Children with acute COVID-19 infrequently experience shock requiring hemodynamic support. However, similar to children with sepsis or septic shock from other causes, children with COVID-19 and shock should be evaluated and managed per the *Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children*.[1,2]

Shock occurs in approximately half of the patients with multisystem inflammatory syndrome in children (MIS-C); reported prevalence ranges from 35% to 80%.[3-5] Limited data inform optimal hemodynamic management for MIS-C. Given that the physiology observed in patients with MIS-C results from a combination of distributive, cardiogenic, and, occasionally, hypovolemic shock, the COVID-19 Treatment Guidelines Panel (the Panel) suggests that clinicians use the management principles outlined in the Surviving Sepsis Campaign's guidelines for children, as well as the principles for clinical management of heart failure and general critical care, as appropriate. The Panel's recommendations apply to the care of children and infants >37 weeks gestational age.

Recommendation

- For children with COVID-19 or MIS-C and shock, the COVID-19 Treatment Guidelines Panel (the Panel) recommends a target mean arterial pressure (MAP) between the fifth and fiftieth, or greater than the fiftieth, percentiles for age **(AIII)**.

Rationale

There are no clinical trials that support specific hemodynamic targets for children with septic shock due to COVID-19, MIS-C, or any other etiology. The panel members for the pediatric Surviving Sepsis Campaign guidelines were divided on the most appropriate MAP target and made no specific recommendation for a target MAP. Therefore, for children with COVID-19 or MIS-C, clinicians should use the same approach used for children without COVID-19 and target a MAP between the fifth and fiftieth, or greater than the fiftieth, percentiles for age. When MAP cannot be reliably measured, systolic blood pressure is a reasonable alternative.[2]

Recommendation

- The Panel recommends that, when available, a combination of serial clinical assessments; cardiac ultrasound or echocardiography; and/or laboratory markers, including lactate levels, should be used to monitor the response to resuscitation in children with COVID-19 or MIS-C and shock **(BIII)**.

Rationale

Observational data from children with non-COVID-19-related sepsis suggest that using clinical assessment alone limits the ability to classify patients with sepsis as having "warm" (i.e., likely to require fluid or vasopressors) or "cold" (i.e., likely to require inotropes) shock, when compared with assessments that include objective measures of cardiac output/index or systemic vascular resistance.[6,7] Cardiac ultrasonography can be performed at the bedside and serially, and it may provide additional clinical data on volume responsiveness and cardiac function.[8] Data from studies evaluating use of cardiac ultrasound in children with COVID-19 and MIS-C are limited to reports from case series.[9] However, given the spectrum of hemodynamic perturbations observed and because approximately a third of children with MIS-C exhibit left ventricular dysfunction, cardiac ultrasonography may have

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particular value in MIS-C.[4]

Elevated lactate level is associated with worse outcomes in children with non-COVID-19-related sepsis, although the specific threshold is unknown and has varied from 2 mmol/L to 4 mmol/L across studies.[10,11] Data on serial lactate measures are limited to a single observational study demonstrating an association between normalization in lactate and a decreased risk of persistent organ dysfunction in children with non-COVID-19-related sepsis (adjusted relative risk 0.47; 95% CI, 0.29–0.78).[12] The role of serial lactate measures has not been systematically evaluated for COVID-19 or MIS-C. An observational study of 1,080 children with MIS-C demonstrated an association between elevated markers of inflammation (e.g., C-reactive protein, procalcitonin), brain natriuretic peptide (BNP) or N-terminal proBNP (NT-proBNP), and troponin and the presence of cardiac dysfunction, shock, and the need for intensive care unit admission. However, the timing of the laboratory values in the study was not available, so the elevated markers may reflect, rather than predict, severe illness.[3]

Recommendation

- The Panel recommends administration of balanced **crystalloids** rather than 0.9% saline for the initial resuscitation of children with shock due to COVID-19 or MIS-C **(CIIb)**.

Rationale

No published clinical trials directly compare balanced/buffered crystalloids with 0.9% saline administered to children with sepsis of any etiology, although an international randomized trial is underway (ClinicalTrials.gov Identifier NCT04102371). Two observational studies using administrative data compared the use of balanced/buffered crystalloids to 0.9% saline in propensity-matched cohorts of children with non-COVID-19-related severe sepsis or septic shock. One of the studies compared patients who received any or only Ringer's lactate solution in the first 3 days of admission with patients who received only normal saline. The study demonstrated no differences between the arms for 30-day mortality or frequency of acute kidney injury.[13]

The other study compared patients receiving only balanced fluids with those receiving only 0.9% saline. The study demonstrated that the balanced-fluid arm had lower mortality (12.5% vs. 15.9%; OR 0.76; 95% CI, 0.62–0.93; $P = 0.007$), reduced acute kidney injury (16.0% vs. 19.2%; OR 0.82; 95% CI, 0.68–0.98; $P = 0.028$), and fewer days on vasoactive infusions (3.0 days vs. 3.3 days; $P < 0.001$) than the saline arm.[14] No published studies focused on patients with COVID-19 or MIS-C, although hyponatremia is common in patients with MIS-C, and decisions about the type of fluid therapy used should be individualized for this population.

Recommendations

- The Panel recommends the use of **epinephrine** or **norepinephrine** rather than dopamine in children with COVID-19 or MIS-C and shock **(BIIa)**.
- There is insufficient evidence to differentiate between norepinephrine or epinephrine as a first-line vasoactive drug in children with COVID-19 or MIS-C. The choice of vasoactive agent should be individualized and based on clinical examination, laboratory data, and data from cardiac ultrasound or echocardiography.

Rationale

Use of vasoactive infusions should be considered for children with shock due to COVID-19 if signs of shock persist after resuscitation with 40 mL/kg to 60 mL/kg of fluid, or sooner if there is evidence of cardiac dysfunction or signs of fluid overload (e.g., tachypnea, hepatomegaly). Similar principles may

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be applied to patients with MIS-C, particularly because their clinical presentation overlaps significantly with the clinical presentation of children with septic shock due to other causes. However, given the high prevalence of cardiac dysfunction in patients with MIS-C, clinicians should consider performing echocardiography or cardiac ultrasound early in the initial resuscitation if MIS-C is suspected and consider initiating a vasoactive infusion if cardiac dysfunction is identified.

Data from pediatric studies comparing vasopressors are limited, and there are no data specific to patients with COVID-19 or MIS-C. Two small pediatric trials compared epinephrine with dopamine in patients with non-COVID-19-related fluid-refractory septic shock.[15,16] One study randomized 63 children to receive dopamine 5 µg/kg/min to 10 µg/kg/min and 57 children to receive epinephrine 0.1 µg/kg/min to 0.3 µg/kg/min. Mortality by Day 28 was 14.2% in the dopamine arm and 7% in the epinephrine arm (OR 6.5; 95% CI, 1.1–37.8; $P = 0.03$). In the other study, 31 children were randomized to receive incremental doses of dopamine 10 µg/kg/min to 20 µg/kg/min, and 29 children were randomized to receive incremental doses of epinephrine 0.1 to 0.3 µg/kg/min. The primary outcome of shock resolution within 1 hour occurred in 4 children (13%) receiving dopamine and 12 children (41%) receiving epinephrine (OR 4.8; 95% CI, 1.3–17.2; $P = 0.019$).

No pediatric trials have compared norepinephrine to other vasoactive agents in patients with sepsis, but based on data from studies of adults, the pharmacologic properties of norepinephrine and dopamine (see Hemodynamics for Adults), and the 2020 Surviving Sepsis Campaign guidelines for children, norepinephrine is suggested over dopamine.[2]

Collectively, this evidence is insufficient to recommend norepinephrine versus epinephrine as a first-line vasoactive agent in children with COVID-19 or MIS-C. Further, given the varied physiology observed with MIS-C in particular, decisions about which vasopressor to use should be individualized based on clinical and laboratory data and findings from bedside cardiac ultrasound or echocardiography.

Recommendation

- There is insufficient evidence for the Panel to recommend either for or against the use of inodilators (including dobutamine or milrinone) in children with COVID-19 or MIS-C who show evidence of cardiac dysfunction and persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents.

Rationale

Data from studies evaluating use of inodilators in children with COVID-19, MIS-C, and non-COVID-19-related sepsis are limited to reports from case series. However, the majority of the pediatric Surviving Sepsis Campaign guidelines panel (77%) would use an inodilator at least some of the time for patients with non-COVID-19-related sepsis, cardiac dysfunction, and persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents.[2] Expert consultation from specialists in pediatric cardiology and critical care medicine is recommended in this scenario.

Additional Recommendations

- For the acute resuscitation of children with COVID-19 or MIS-C and shock, the Panel recommends the use of **crystalloids** rather than albumin **(AIIb)**.
- The Panel **recommends against** using **hydroxyethyl starches** for intravascular volume replacement in children with COVID-19 or MIS-C and sepsis or septic shock **(AIII)**.
- For children with refractory shock who have recently completed a course of corticosteroids to treat COVID-19, the Panel recommends using low-dose corticosteroid therapy ("shock-reversal") over

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no corticosteroid therapy **(CIII)**.

- Children who are currently receiving corticosteroids for COVID-19 or MIS-C are generally receiving sufficient glucocorticoid replacement therapy and do not require additional hydrocortisone for refractory shock.

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Oxygenation and Ventilation for Children

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The COVID-19 Treatment Guidelines Panel's (the Panel) recommendations in this section were informed by recommendations from the Surviving Sepsis Campaign's guidelines for managing adult sepsis, pediatric sepsis, and COVID-19, as well as by recommendations from the 2015 Pediatric Acute Lung Injury Consensus Conference (PALICC).

Goal of Oxygenation

Recommendations

- An oxygen saturation (SpO_2) target of 92% to 97% is recommended for most children with COVID-19 who require supplemental oxygen **(AIIb)**.
- For children with severe pediatric acute respiratory distress syndrome (PARDS; i.e., with an oxygenation index ≥16 or SpO_2 index ≥12.3), an SpO_2 of <92% can be considered to minimize exposure to a high fraction of inspired oxygen (FiO_2), but prolonged periods of SpO_2 <88% should be avoided **(CIII)**.

Rationale

The optimal SpO_2 in children with COVID-19 is unknown. However, there is no evidence that the target SpO_2 should differ from the 2015 PALICC recommendation.[1] An SpO_2 of 92% to 97% is recommended for most children with COVID-19 who require supplemental oxygen. The potential harm of hyperoxia in children was demonstrated in a recent meta-analysis of 11 observational studies of children without COVID-19.[2] The study demonstrated that critically ill children with hyperoxia had greater odds of mortality than those without hyperoxia (OR 1.59; 95% CI, 1.00–2.51). However, there was significant heterogeneity across the included studies for populations, definitions of hyperoxia, and the timing of assessment for mortality outcomes. For children with severe PARDS (i.e., with an oxygenation index ≥16 or SpO_2 index ≥12.3),[1] an SpO_2 <92% can be considered to minimize exposure to a high FiO_2. Although no evidence clearly identifies a safe minimum SpO_2 in children, prolonged exposure to SpO_2 <88% should be avoided. When SpO_2 is <92%, monitoring oxygen delivery markers, including central venous SpO_2, is suggested.[3]

High-Flow Nasal Cannula Oxygen and Noninvasive Ventilation for Children With COVID-19 and Acute Respiratory Failure

Recommendation

- For infants and children with COVID-19 and persistent respiratory failure despite conventional oxygen therapy who have no indicators for endotracheal intubation, a time-limited trial of noninvasive ventilation (NIV) or high-flow nasal cannula (HFNC) oxygen is recommended **(AIIa)**. There is insufficient evidence for the Panel to recommend either for or against the use of HFNC oxygen over NIV or the use of NIV over HFNC oxygen in infants and children with COVID-19.

Rationale

No high-quality studies evaluate the use of HFNC oxygen or NIV in children with COVID-19. Therefore, when choosing a mode of respiratory support for children with COVID-19, the principles of management used for patients without COVID-19 should be followed. Both the *Surviving Sepsis*

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Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children and PALICC recommend the use of NIV for children with respiratory failure who have no indication for intubation.[4,5]

Furthermore, the response to NIV, particularly for children with more severe hypoxemia or high work of breathing, should be gauged early (within the first several hours). If the patient does not show improvement, intubation should be considered. To unload respiratory muscles, bilevel modes of NIV (with inspiratory pressure augmentation, such as BiPAP), if tolerated, are preferred over the use of continuous positive airway pressure (CPAP) alone, although CPAP is an alternative for children who cannot achieve an adequate seal with the NIV interface or who have significant patient-ventilator asynchrony.[4]

HFNC oxygen is a relatively new, but increasingly used, mode of respiratory support for infants and children with acute respiratory failure.[6] Data from studies evaluating the effectiveness of HFNC oxygen relative to NIV or conventional oxygen are limited to studies of children with pneumonia in limited-resource settings and studies of children with bronchiolitis. Two randomized controlled trials of children with pneumonia were conducted in limited-resource settings. One study demonstrated a slightly lower relative risk of mortality with the use of HFNC oxygen when compared with conventional oxygen therapy (adjusted HR 0.79; 95% CI, 0.54–1.16), although the results were not statistically significant.[7] The other trial demonstrated that children treated with bubble CPAP ventilation had a lower proportion of mortality than children who received low-flow oxygen (relative risk 0.25; 95% CI, 0.07–0.89; $P = 0.02$).[8] The results also indicated that for the composite outcome of treatment failure, there was no difference between the use of HFNC oxygen and bubble CPAP (relative risk 0.50; 99.7% CI, 0.11–2.29).

A randomized, noninferiority trial compared HFNC oxygen (2 L/kg/min) and nasal CPAP among 142 infants aged <6 months with bronchiolitis not caused by COVID-19.[9] The primary outcome was treatment failure within 24 hours, defined as an increase of ≥1 point in the modified Wood's Clinical Asthma Score (M-WCAS) or Échelle Douleur Inconfort Nouveau-Né (EDIN) score (a neonatal pain and discomfort scale), a respiratory rate >60 breaths/min and an increase of >10 breaths/min from baseline, or >2 severe apnea episodes per hour. Treatment failure occurred more often in the HFNC oxygen arm than in the nasal CPAP arm (51% vs. 31%), a result that failed to meet the prespecified noninferiority margin. Notably, in the HFNC arm, 72% of the patients who had treatment failure were managed successfully with nasal CPAP, and there were no differences between the arms for intubation rates or length of stay.

A systematic review of the noninferiority trial and 2 smaller trials comparing HFNC to nasal CPAP summarized the results of 213 infants and children aged ≤2 years with bronchiolitis.[10] Treatment failure in the 2 smaller trials was rare, and no differences were detected between the HFNC and nasal CPAP arms for any of the clinical outcomes.[11,12]

In a study that assessed whether higher flow rates of HFNC oxygen improved outcomes, 286 infants aged ≤6 months and with severe bronchiolitis were randomized to receive HFNC oxygen 2 L/kg/min or HFNC oxygen 3 L/kg/min.[13] The primary outcome of treatment failure (i.e., an increase of ≥1 point in M-WCAS or EDIN score, a respiratory rate >60 breaths/min and an increase of >10 breaths/min from baseline, or >2 severe apnea episodes per hour) occurred in 38.7% of the infants in the 2 L/kg/min arm and in 38.9% of the infants in the 3 L/kg/min arm ($P = 0.98$). Patient discomfort, as measured by EDIN score, occurred more often in the 3 L/kg/min arm than in the 2 L/kg/min arm (43% vs. 16%, $P = 0.002$).

HFNC oxygen is increasingly being used in children. These studies highlight the potential role of an HFNC oxygen trial in the management of children with acute respiratory failure due to COVID-19, particularly for infants and young children who may have NIV-related challenges, such as poor mask

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fit, discomfort, or patient-ventilator asynchrony. For the use of HFNC oxygen in children, consider flow rates of up to 2 L/kg/min, with a maximum of 60 L/min. If patients do not improve within the first few hours of receiving HFNC oxygen, their treatment should be escalated to NIV or intubation.

Awake Prone Positioning for Children Not Receiving Mechanical Ventilation

Recommendations

- There is insufficient evidence for the Panel to recommend either for or against a trial of awake prone positioning for children with persistent hypoxemia who require HFNC oxygen or NIV and do not require endotracheal intubation.
- For patients with refractory hypoxemia who meet the indications for intubation and mechanical ventilation, the Panel **recommends against** the use of awake prone positioning as a rescue therapy to avoid intubation **(AIII)**.

Rationale

There are no high-quality pediatric data evaluating the effect of awake prone positioning on clinical outcomes in children with COVID-19 or non-COVID-19-related illness. Awake prone positioning may be considered for older children and adolescents (see Oxygenation and Ventilation for Adults). In addition, pediatric clinicians should consider a child's developmental stage and ability to comply with the protocols for awake prone positioning.

Intubation for Mechanical Ventilation in Children With Acute COVID-19

Recommendations

- If intubation becomes necessary, the Panel recommends that an experienced practitioner perform the procedure in a controlled setting due to the enhanced risk of exposing health care practitioners to SARS-CoV-2 during intubation **(AIII)**.
- The Panel recommends using cuffed endotracheal tubes over uncuffed endotracheal tubes in children who require endotracheal intubation **(AIIb)**.

Rationale

To optimize the safety of patients and health care workers and maximize first-attempt success, intubation should be performed in a controlled setting by an experienced practitioner. In addition, cuffed endotracheal tubes are preferred for children of all ages with COVID-19 to minimize leak around the endotracheal tube, ensure delivery of ventilator pressure, decrease the risk of aspiration, reduce the need for endotracheal tube exchange, and reduce aerosolization of respiratory secretions during mechanical ventilation.[3,14-16]

General Considerations for Children With COVID-19 and PARDS Who Require Mechanical Ventilation

Recommendations

For children with COVID-19 and PARDS who require mechanical ventilation:

- 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) **(AIIb)**.
- The Panel recommends targeting plateau pressures of ≤28 cm H_2O for children with normal chest wall compliance and ≤32 cm H_2O for those with impaired chest wall compliance **(AIII)**.

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- The Panel recommends using a higher positive end-expiratory pressure (PEEP) strategy (i.e., >10–15 cm H_2O or higher in patients with severe PARDS) over a lower PEEP strategy, titrated based on observed responses in oxygenation, hemodynamics, and respiratory system compliance **(BIIb)**.
- The Panel recommends permissive hypercapnia (e.g., pH >7.15 to 7.30), if needed, to remain within lung-protective strategies and to minimize ventilator-associated lung injury, provided the patient does not have a coexisting condition that would be worsened by acidosis (e.g., severe pulmonary hypertension, ventricular dysfunction, intracranial hypertension) **(AIII)**.
- The Panel **recommends against** the routine use of inhaled nitric oxide **(AIII)**.

Rationale

There is no evidence that ventilator management of children with PARDS due to COVID-19 should differ from ventilator management of patients with PARDS due to other causes. The Panel's recommendations are derived from the 2015 PALICC recommendations.[1,3] Since the publication of the PALICC recommendations, no randomized trials have provided significant new evidence, although some observational data support some of the PALICC recommendations.

A large observational study conducted in 71 international pediatric intensive care units identified that for patients with mild to moderate acute respiratory distress syndrome (ARDS), less adherence to the recommended VT of 5 mL/kg to 8 mL/kg (or 3 mL/kg to 6 mL/kg for patients with severe ARDS) was associated with higher mortality and with more time on ventilation.[17] In general, supraphysiologic VT ventilation (>8 mL/kg) should not be used in patients with PARDS, and VT should be adjusted within the acceptable range to maintain other lung-protective ventilation targets (e.g., maintaining ≤28 cm H_2O plateau pressure). The use of ultra-low VT ventilation (<4 mL/kg) has not been systematically studied in children, so it should be used with caution.

The ARDS Network established a ventilator protocol that includes suggested low PEEP/high FiO_2 levels.[18] The protocol suggests that for patients receiving FiO_2 ≥0.6, a PEEP level of ≥10 cm H_2O would be implemented, which aligns with recommendations from PALICC. Two observational studies have identified better clinical outcomes associated with use of the suggested (or higher) PEEP levels compared to lower PEEP levels.[17,19] The multicenter studies, including nearly 1,500 pediatric patients with ARDS, each demonstrated that PEEP levels lower than those recommended by the ARDS Network were associated with higher mortality.

Inhaled nitric oxide can be considered as a rescue therapy for children with severe PARDS and COVID-19. In a small, randomized trial, the use of inhaled nitric oxide resulted in reduced use of extracorporeal membrane oxygenation (ECMO).[20] However, inhaled nitric oxide has a heterogeneous treatment effect, and many patients do not show improved gas exchange. Although adverse effects are rare, use of inhaled nitric oxide can have a substantial effect on health care costs. Therefore, inhaled nitric oxide should not be considered routine therapy for children with PARDS or COVID-19 who are receiving mechanical ventilation.

Fluid Management for Children With PARDS

Recommendation

- Following an initial resuscitation in children with PARDS due to COVID-19, clinicians should monitor and titrate fluid balance to maintain adequate intravascular volume while aiming to prevent positive fluid balance **(BIIb)**.

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Rationale

There is no evidence that fluid management in children with PARDS due to COVID-19 should differ from fluid management in patients with PARDS due to other causes. Therefore, the Panel's recommendation aligns with the PALICC recommendation.[1] No pediatric randomized trials have directly compared a liberal versus conservative fluid strategy in PARDS of any etiology. Several observational studies have demonstrated an association between greater fluid overload and worse clinical outcomes, including fewer ventilator-free days and increased mortality.[21-23]

In a multicenter study of 168 children with acute lung injury, daily and cumulative fluid balance were measured over the first 7 days after participants met the inclusion criteria. After adjustment for demographic characteristics, pediatric risk of mortality III (PRISM III) scores, vasopressor use, and the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2), an increasing cumulative fluid balance on Day 3 was associated with fewer ventilator-free days, but no association with mortality was detected.[21]

A more recent, single-center study including 732 children with acute lung injury demonstrated an association between higher cumulative fluid balance on Days 5 to 7 and increased mortality (for 100 mL/kg on Day 5; OR 1.34; 95% CI, 1.11–1.61) after adjustment for oxygenation index, the number of nonpulmonary organ failures, immunocompromised status, and vasopressor scores. Also, greater cumulative fluid balance on Days 4 to 7 was associated with a lower probability of successful extubation by Day 28.[23] Collectively, the findings from these pediatric observational studies demonstrate the potential harm of fluid overload in children with PARDS, particularly after 3 to 4 days of illness.

These results are consistent with the findings from FACTT, a trial of conservative versus liberal fluid management strategies in adults.[24] In adults, FACTT found no difference between arms for 60-day mortality, but the conservative strategy arm demonstrated improved oxygenation and less time on mechanical ventilation and in the intensive care unit when compared with the liberal strategy arm. However, no analysis of data from prospective pediatric trials delineates a causal relationship between a specific, protocolized, fluid management strategy, or the timing of such a strategy, and clinical outcomes. Therefore, an individualized fluid management approach that is titrated to maintain intravascular volume while preventing excessive positive fluid balance, as suggested by the 2015 PALICC recommendation, is appropriate.[1]

Neuromuscular Blockade for Mechanically Ventilated Children With Severe PARDS

Recommendation

- For mechanically ventilated children with severe PARDS and COVID-19, the Panel recommends minimal yet effective use of neuromuscular blocking agents in conjunction with sedation, if sedation alone is inadequate to achieve lung-protective ventilation **(BIII)**.

Rationale

There is no evidence that the use of neuromuscular blockade in children with COVID-19 should differ from practices used for severe PARDS from other causes. Therefore, the Panel's recommendation aligns directly with the PALICC recommendation.[1] Since the publication of the 2015 PALICC recommendation, no new data support significant changes to the recommendation.

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Therapies for Mechanically Ventilated Children With Severe PARDS and Refractory Hypoxemia

Recommendations

For children with severe PARDS and refractory hypoxemia after other oxygenation strategies have been optimized:

- The Panel recommends inhaled nitric oxide as a rescue therapy; if no rapid improvement in oxygenation is observed, inhaled nitric oxide should be discontinued **(BIIb)**.
- The Panel recommends prone positioning for 12 to 16 hours per day over no prone positioning **(BIII)**.
- There is insufficient evidence for the Panel to recommend either for or against the use of recruitment maneuvers, but if they are used in children, slow, incremental and decremental adjustments in PEEP are preferred to sustained inflation maneuvers.
- There is insufficient evidence for the Panel to recommend either for or against the use of high-frequency oscillatory ventilation (HFOV) in children with PARDS.

Rationale

There is no evidence that the use of inhaled nitric oxide, prone positioning, or HFOV in children with COVID-19 should differ from practices used for severe PARDS from other causes. Therefore, the Panel's recommendations are largely based on PALICC recommendations.[1] Since the publication of the 2015 PALICC recommendations, many new trials evaluating these practices have been conducted.

One randomized controlled trial and 2 propensity-matched, observational studies have evaluated the use of inhaled nitric oxide in PARDS since the publication of the PALICC recommendations. The randomized controlled trial included 55 patients and found that the use of inhaled nitric oxide resulted in no statistical difference between arms for 28-day mortality (8% mortality in the inhaled nitric oxide arm vs. 28% in the placebo arm), although the trial was underpowered for this outcome.[20] However, the inhaled nitric oxide arm had approximately 5 more ventilator-free days than the placebo arm, a result that was primarily mediated by avoiding the use of ECMO. These results have been corroborated by observational studies, which also reported more ventilator-free days for patients who received inhaled nitric oxide.[25,26] Although the evidence is insufficient to recommend the use of inhaled nitric oxide for all patients with ARDS, in cases of severe hypoxemia, it can be considered as a rescue therapy to potentially avoid the use of ECMO.

No new studies have evaluated the role of prone positioning in PARDS, although a large, multicenter trial is ongoing. Therefore, the Panel's recommendation to consider prone positioning in cases of severe PARDS aligns with the PALICC recommendation and is supported by adult data, primarily from PROSEVA, a trial on prone positioning in patients with ARDS.[27]

The 2015 PALICC recommendations included the use of careful recruitment maneuvers with incremental and decremental adjustments in PEEP.[1] In children, this approach to recruitment maneuvers is preferred over sustained inflation maneuvers due to the increased risk of harm from barotrauma and hemodynamic compromise in patients with sustained inflation. Clinical trials in adults have highlighted the potential harm from recruitment maneuvers applied to patients who may not have recruitable lung.[28,29] Therefore, although there is insufficient evidence to recommend for or against the use of recruitment maneuvers in children with refractory hypoxemia, if recruitment maneuvers are used, the preferred strategy is slow, incremental increases and decreases of PEEP.

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Since the publication of the 2015 PALICC recommendations, 2 small randomized controlled trials have examined the use of HFOV for PARDS.[30,31] Neither study found a significant difference for mortality. Several observational studies using propensity matching have shown either no difference in outcomes between the HFOV and conventional ventilation arms or a potential for higher mortality or a longer ventilation time with the use of HFOV, when compared with conventional ventilation.[32-36] In some of these analyses, residual confounding has been a concern. A large, multicenter randomized controlled trial of HFOV for PARDS is ongoing. Therefore, the Panel has determined that there is insufficient evidence to recommend for or against the use of HFOV in COVID-19-related PARDS. Some concerns have been raised about the use of HFOV and aerosolization of COVID-19, although adding a filter to the expiratory limb of the HFOV circuit may alleviate these concerns.

Multisystem Inflammatory Syndrome in Children

More than half of the patients with multisystem inflammatory syndrome in children (MIS-C) require mechanical ventilation or NIV.[37-39] For these patients with MIS-C, the indications for mechanical ventilation vary and include shock or cardiac dysfunction, pulmonary edema, procedural preparation (e.g., to facilitate sedation for central venous catheter placement), respiratory failure, or neurologic failure. The management of oxygenation and ventilation in children with MIS-C should follow the usual principles of shock management outlined in the Surviving Sepsis Campaign guidelines for children, as well as the principles for clinical management of heart failure and general critical care, as appropriate.[5]

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Extracorporeal Membrane Oxygenation for Children

Last Updated: May 31, 2022

Recommendation

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends that the use of extracorporeal membrane oxygenation (ECMO) should be considered for children with acute COVID-19 or multisystem inflammatory syndrome in children (MIS-C) who have refractory hypoxemia or shock when hemodynamic parameters cannot be maintained or lung-protective strategies result in inadequate gas exchange **(CIII)**. Candidacy for ECMO should be determined on a case-by-case basis by the multidisciplinary team.

Rationale

ECMO is used as a rescue therapy for children with refractory hypoxemia or shock. Similar to outcomes for adults, outcomes for children managed with venovenous ECMO are variable and are influenced by the etiology and duration of respiratory failure and by underlying comorbid medical conditions.[1,2] In addition, studies have shown that pediatric centers that treat fewer patients with ECMO have worse outcomes than facilities that treat a high volume of patients with ECMO.[3,4] No randomized trials evaluate the efficacy or benefit of ECMO for hypoxemic respiratory failure in children without COVID-19 beyond the neonatal period. In an observational study of 122 children with severe pediatric acute respiratory distress syndrome (PARDS), 90-day mortality for children treated with ECMO and for those supported without ECMO was similar (25% vs. 30%).[5]

The Pediatric Acute Lung Injury Consensus Conference recommends considering ECMO for patients with severe PARDS from reversible causes or for children who are candidates for lung transplantation.[6] The *Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children* issued a weak recommendation, based on very low quality of evidence, to use venovenous ECMO for children with PARDS and refractory hypoxemia.[7]

Venoarterial ECMO has been used successfully for the treatment of refractory shock in children, although no trials evaluate this approach, and the potential benefits must be weighed against risks of bleeding or thromboembolic events.[8-10] The Surviving Sepsis Campaign guidelines for children issued a weak recommendation, based on very low quality of evidence, for use of venoarterial ECMO in children with shock that is refractory to all other treatments; however, a standardized definition of refractory shock in children is not available.[7]

Studies evaluating data on the use of ECMO in children with COVID-19 and MIS-C are limited to case reports and case series.[11-13] A publicly available registry for pediatric patients with COVID-19 on ECMO is maintained by the multinational Extracorporeal Life Support Organization (ELSO). In-hospital mortality at 90 days was about 30%, which is similar to reports from non-COVID-19 ECMO cohorts.[14,15] ELSO has published guidelines for use of ECMO in COVID-19.[16] In general, ECMO candidacy for children with COVID-19 or MIS-C should be assessed using criteria similar to those used for other causes of severe respiratory failure or shock. Cannulation approaches and management principles should follow published international guidelines and local protocols for non-COVID-19 patients.

Pediatric clinicians should consider entering patients into clinical trials or registries to inform future recommendations regarding use of ECMO in children with COVID-19. The following resources provide more information on an international ECMO registry and on clinical trials evaluating ECMO in children with COVID-19:

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- The ELSO registry for ECMO in COVID-19
- ClinicalTrials.gov

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

Last Updated: April 29, 2022

Summary Recommendations

Remdesivir is the only drug that is approved by the Food and Drug Administration (FDA) for the treatment of COVID-19. Ritonavir-boosted nirmatrelvir (Paxlovid), molnupiravir, and certain anti-SARS-CoV-2 monoclonal antibodies (mAbs) have received Emergency Use Authorizations from the FDA for the treatment of COVID-19.
 	
This section focuses on the COVID-19 Treatment Guidelines Panel's (the Panel) recommendations for using small-molecule antiviral drugs to treat COVID-19. These recommendations are based on the available data; for more information, see Table 2f. For recommendations and information regarding the use of anti-SARS-CoV-2 mAbs, see Anti-SARS-CoV-2 Monoclonal Antibodies and Table 3c.
 	
Recommendations for Treating Nonhospitalized Patients
• The Panel recommends the use of the following anti-SARS-CoV-2 therapies as preferred treatments for COVID-19. These drugs are listed in order of preference:
  • **Ritonavir-boosted nirmatrelvir (Paxlovid) (AIIa)**
  • **Remdesivir (BIIa)**
• The Panel recommends the use of the following anti-SARS-CoV-2 therapies as alternative treatments for COVID-19 **ONLY** when neither of the preferred therapies are available, feasible to use, or clinically appropriate. These drugs are listed in alphabetical order:
  • **Bebtelovimab (CIII)**
  • **Molnupiravir (CIIa)**
• See Therapeutic Management of Nonhospitalized Adults With COVID-19 for detailed recommendations.
 	
Recommendations for Treating Hospitalized Patients
• See Therapeutic Management of Hospitalized Adults With COVID-19 for the Panel's recommendations on using remdesivir with or without immunomodulators in certain hospitalized patients.
 	
Antiviral Drugs That the Panel Recommends Against
• The Panel **recommends against** the use of the following drugs for the treatment of COVID-19, except in a clinical trial:
  • **Interferons** for nonhospitalized patients **(AIIa)**
  • **Interferon alfa** or **lambda** for hospitalized patients **(AIIa)**
  • **Ivermectin (AIIa)**
  • **Nitazoxanide (BIIa)**
• The Panel **recommends against** the use of the following drugs for the treatment of COVID-19:
  • **Chloroquine** or **hydroxychloroquine** and/or **azithromycin** for hospitalized **(AI)** and nonhospitalized patients **(AIIa)**
  • **Lopinavir/ritonavir** and **other HIV protease inhibitors** for hospitalized **(AI)** and nonhospitalized patients **(AIII)**
  • **Systemic interferon beta** for hospitalized patients **(AI)**

Rating of Recommendations: A = Strong; B = Moderate; C = Weak **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 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 prevent viral replication

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through various mechanisms, including blocking SARS-CoV-2 entry, inhibiting the activity of SARS-CoV-2 3-chymotrypsin-like protease (3CLpro) and RNA-dependent RNA polymerase (RdRp), and causing lethal viral mutagenesis.[1-3] 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.[4] 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 a nucleotide prodrug of an adenosine analog. It binds to the viral RNA-dependent RNA polymerase and inhibits viral replication by terminating RNA transcription prematurely. Remdesivir has demonstrated in vitro activity against 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 expected to be active against the B.1.1.529 (Omicron) variant of concern.[3,4]

Intravenous remdesivir is approved by the Food and Drug Administration (FDA) for the treatment of COVID-19 in adult and pediatric patients (aged ≥12 years and weighing ≥40 kg). It is approved for the treatment of mild to moderate COVID-19 in high-risk, nonhospitalized patients (i.e., a 3-day course initiated within 7 days of symptom onset) and for the treatment of hospitalized patients with COVID-19 (i.e., a 5-day course).[5] See Table 2f for more information. It is also available through an FDA Emergency Use Authorization (EUA) for the treatment of COVID-19 in nonhospitalized and hospitalized pediatric patients weighing 3.5 kg to <40 kg or aged <12 years and weighing ≥3.5 kg.

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.

Recommendations

For the Panel's recommendations and information on the clinical efficacy of remdesivir in high-risk, nonhospitalized patients with mild to moderate COVID-19 and on the order of preference for outpatient antiviral therapies, see Therapeutic Management of Nonhospitalized Adults With COVID-19. There are no data on the use of combination antiviral therapies or the combination of antiviral agents and anti-SARS-CoV-2 monoclonal antibodies for the treatment of nonhospitalized patients with COVID-19. Clinical trials are needed to determine whether combination therapy has a role in the treatment of COVID-19.

For the Panel's recommendations and information on the clinical efficacy of remdesivir with or without immunomodulators in certain hospitalized patients, see Therapeutic Management of Hospitalized Adults With COVID-19. Data on the safety and efficacy of using remdesivir in combination with corticosteroids are primarily derived from observational studies, with some (but not all) of these studies suggesting that remdesivir plus dexamethasone provides a clinical benefit for hospitalized patients with COVID-19.[6-8]

In the CATCO study, patients hospitalized with COVID-19 were randomized to receive remdesivir plus standard care or standard care alone. Among patients who were not receiving mechanical ventilation at baseline, remdesivir significantly reduced the need for mechanical ventilation. About 87% of participants in the trial received corticosteroids as part of their standard care.[9]

Remdesivir plus dexamethasone has not been directly compared to dexamethasone alone in a large randomized trial. However, there are theoretical reasons that combination therapy may be beneficial for some patients with severe COVID-19. Remdesivir has also been studied in combination with other immunomodulators, including baricitinib[10] and tocilizumab.[11]

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Monitoring and Adverse Effects

Remdesivir can cause gastrointestinal symptoms (e.g., nausea), elevated transaminase levels, an increase in prothrombin time without a change in the international normalized ratio, and hypersensitivity reactions.

Before starting patients on remdesivir, it is recommended that estimated glomerular filtration rate (eGFR), liver function, and prothrombin time tests be performed as clinically appropriate and be repeated during treatment as clinically indicated. However, it should be noted that in the PINETREE study, in which outpatients with mild to moderate COVID-19 received remdesivir for 3 days, baseline serum creatinine was not required in patients weighing >48 kg.[12] Remdesivir may need to be discontinued if a patient's alanine transaminase (ALT) level increases to >10 times the upper limit of normal, and it should be discontinued if increases in ALT levels and signs or symptoms of liver inflammation are observed.[5]

Remdesivir should be administered in a setting where severe hypersensitivity reactions, such as anaphylaxis, can be managed and the emergency medical system can be activated. Patients should be monitored during the infusion and observed for at least 1 hour after the infusion as clinically appropriate.

Patients who are severely immunocompromised may have prolonged SARS-CoV-2 replication, which may lead to rapid viral evolution. There is a theoretical concern that the use of a single antiviral agent in these patients may result in the emergence of resistant virus. Additional studies are needed to assess this risk. The role of combination antiviral therapy is not yet known.

Considerations in Patients With Renal Insufficiency

Each 100 mg vial of remdesivir lyophilized powder contains 3 g of sulfobutylether beta-cyclodextrin sodium (SBECD), and each 100 mg/20 mL vial of remdesivir solution contains 6 g of SBECD.[5] SBECD is a vehicle that is primarily eliminated through the kidneys. A patient with COVID-19 who receives a loading dose of remdesivir 200 mg would receive 6 g to 12 g of SBECD, depending on the formulation. This amount of SBECD is within the safety threshold for patients with normal renal function.[13] Accumulation of SBECD in patients with renal impairment may result in liver and renal toxicities. Clinicians may consider preferentially using the lyophilized powder formulation (which contains less SBECD) in patients with renal impairment.

Because both remdesivir formulations contain SBECD, patients with an eGFR of <50 mL/min were excluded from some clinical trials of remdesivir; other trials had an eGFR cutoff of <30 mL/min. The FDA product label does not recommend using remdesivir in patients with an eGFR of <30 mL/min due to a lack of data.[14]

In 2 observational studies that evaluated the use of the solution formulation of remdesivir (not the reconstituted lyophilized powder formulation) in hospitalized patients with COVID-19, no significant differences were reported in the incidences of adverse effects or acute kidney injury between patients with an estimated creatinine clearance (CrCl) of <30 mL/min and those with an estimated CrCl of ≥30 mL/min.[15,16] In 1 study, 20 patients had an estimated CrCl of <30 mL/min and 115 had an estimated CrCl of ≥30 mL/min;[15] the other study included 40 patients who had an estimated CrCl of <30 mL/min and 307 patients who had an estimated CrCl of ≥30 mL/min.[16] These observational data suggest that remdesivir can be used in patients with an eGFR of <30 mL/min if the potential benefits outweigh the risks.

Drug-Drug Interactions

Currently, no clinical drug-drug interaction studies of remdesivir have been conducted. In vitro, remdesivir is a minor substrate of cytochrome P450 (CYP) 3A4 and a substrate of the drug transporters

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organic anion transporting polypeptide (OATP) 1B1 and P-glycoprotein. It is also an inhibitor of CYP3A4, OATP1B1, OATP1B3, and multidrug and toxin extrusion protein 1 (MATE1).[5]

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).

See Table 2f for more information.

Considerations in Pregnancy

Remdesivir should not be withheld from pregnant patients if it is otherwise indicated.

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 remdesivir use in pregnant patients from small studies and case reports are reassuring.[17] 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 effects.[18]

Considerations in Children

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 or in nonhospitalized pediatric patients with mild to moderate COVID-19 and at high risk for disease progression. There are insufficient data on the safety and efficacy of using remdesivir to treat COVID-19 in hospitalized or nonhospitalized pediatric patients aged <12 years or weighing <40 kg, because these populations have not been evaluated in clinical trials for remdesivir. The limited data from the compassionate use program and small-case series suggest that remdesivir was well-tolerated in children who met the EUA criteria, but the data on young infants and neonates are extremely limited.[19-23] A clinical trial is currently evaluating the pharmacokinetics of remdesivir in children (ClinicalTrials.gov Identifier NCT04431453).

Clinical Trials

Several clinical trials that are evaluating the use of 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

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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 the randomized controlled trials that have had the greatest impact on the Panel's recommendations. Studies of hospitalized patients are listed first, followed by studies of nonhospitalized patients.

Methods	Results	Limitations and Interpretation
ACTT-1: Multinational, Placebo-Controlled, Double-Blind RCT of Remdesivir in Hospitalized Patients With COVID-19[1]		

Key Inclusion Criteria:
• Laboratory-confirmed SARS-CoV-2 infection
• ≥1 of the following criteria:
  • Pulmonary infiltrates
  • SpO_2 ≤94% on room air
  • Need for supplemental oxygen, high-flow oxygen, NIV, MV, or ECMO
Key Exclusion Criteria:
• ALT or AST >5 times ULN
• eGFR <30 mL/min
• Pregnancy or breastfeeding
Interventions:
• RDV 200 mg IV on Day 1, then RDV 100 mg daily for up to 9 more days (n = 541)
• Placebo for up to 10 days (n = 521)
Primary Endpoint:
• Time to clinical recovery
Key Secondary Endpoints:
• Clinical status at Day 15, as measured by an OS
• Mortality by Day 29
• Occurrence of SAEs
	Participant Characteristics:
	• Mean age 58.9 years
	• 53.3% White, 21.3% Black, 12.7% Asian, 23.5% Hispanic/Latinx
	• Coexisting conditions: 26.2% with 1; 55.2% with ≥2
	• 13.0% not on oxygen; 41.0% on supplemental oxygen; 18.2% on high-flow oxygen or NIV; 26.8% on MV or ECMO
	• Median time from symptom onset to randomization: 9 days (IQR 6–12 days)
	• Received corticosteroids during study: 21.6% in RDV arm; 24.4% in placebo arm
	Primary Outcomes:
	• Time to clinical recovery: 10 days in RDV arm vs. 15 days in placebo arm (rate ratio for recovery 1.29; 95% CI, 1.12–1.49; $P < 0.001$)
	• Benefit of RDV greatest in patients randomized during first 10 days after symptom onset and those who required supplemental oxygenation at enrollment
	• No difference in time to recovery for patients on high-flow oxygen, NIV, MV, or ECMO at enrollment
	Secondary Outcomes:
	• Clinical status at Day 15: improvement more likely in RDV arm (OR 1.5; 95% CI, 1.2–1.9; $P < 0.001$)
	• Mortality by Day 29: no difference between arms
	• Proportion of patients with SAEs: similar between arms (25% vs. 32%)
		Key Limitations:
		• Wide range of disease severity among patients; study not powered to detect differences within subgroups
		• Powered to detect differences in clinical improvement, not mortality
		• No data on longer-term morbidity
		Interpretation:
		• In patients with severe COVID-19, RDV reduced time to clinical recovery.
		• The benefit was most apparent in hospitalized patients who were receiving supplemental oxygen.
		• There was no observed benefit in those on high-flow oxygen, NIV, MV, or ECMO, but study was not powered to detect differences within subgroups.

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Methods	Results	Limitations and Interpretation
DisCoVeRy: Open-Label, Adaptive RCT of Remdesivir in Hospitalized Patients With Moderate or Severe COVID-19 in Europe[2]		
Key Inclusion Criteria: • Laboratory-confirmed SARS-CoV-2 infection • Illness of any duration • SpO_2 ≤94% on room air or use of supplemental oxygen, high-flow oxygen devices, NIV, or MV **Key Exclusion Criteria:** • ALT or AST >5 times ULN • Severe chronic kidney disease **Interventions:** • RDV 200 mg IV on Day 1, then RDV 100 mg IV once daily for up to 9 days (n = 429) • SOC (n = 428) **Primary Endpoint:** • Clinical status at Day 15, as measured by an OS **Key Secondary Endpoints:** • Mortality at Day 29 • Occurrence of SAEs	**Participant Characteristics:** • Median age 64 years; 70% men; 69% White • 74% with ≥1 coexisting condition • 40% received corticosteroids during study • Median days from symptom onset to randomization: 9 days in both arms • 61% with moderate disease; 39% with severe disease **Primary Outcomes:** • Clinical status at Day 15: no difference between arms (OR 0.98; 95% CI, 0.77–1.25; $P = 0.85$) • A prespecified subgroup analysis based on duration of symptoms found no significant difference in clinical status between arms. **Secondary Outcomes:** • Mortality: no difference between arms (8% in RDV arm vs. 9% in SOC arm) • Proportion of patients with SAEs: no difference between arms (33% in RDV arm vs. 31% in SOC arm; $P = 0.48$)	**Key Limitations:** • Open-label study • 440 participants in this study also enrolled in the WHO Solidarity trial. **Interpretation:** • There was no clinical benefit of RDV in hospitalized patients who were symptomatic for >7 days and who required supplemental oxygen.
WHO Solidarity Trial: Multinational, Open-Label, Adaptive RCT of Repurposed Drugs in Hospitalized Patients With COVID-19[3]		
Key Inclusion Criteria: • Aged ≥18 years • Not known to have received any study drug • Not expected to be transferred elsewhere within 72 hours **Interventions:** • RDV 200 mg IV on Day 0, then RDV 100 mg daily on Days 1–9 (n = 2,743) • Local SOC (n = 2,708) **Primary Endpoint:** • In-hospital mortality **Key Secondary Endpoint:** • Initiation of MV	**Participant Characteristics:** • 47% aged 50–69 years; 18% aged ≥70 years • At entry: 67% on supplemental oxygen; 9% on MV • Rates of comorbidities similar between arms • 48% in both arms received corticosteroids during study **Primary Outcome:** • In-hospital mortality: 11.0% in RDV arm vs. 11.2% in SOC arm (rate ratio 0.95; 95% CI, 0.81–1.11) **Secondary Outcome:** • Initiation of MV: 10.8% in RDV arm vs. 10.5% in SOC arm	**Key Limitations:** • Open-label design limits ability to assess time to recovery, as RDV may have been continued even if patient improved. • No data on time from symptom onset to enrollment • No assessment of outcomes post hospital discharge **Interpretation:** • RDV did not decrease in-hospital mortality or the need for MV compared to SOC.

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Methods	Results	Limitations and Interpretation
GS-US-540-5774 Study: Multinational, Open-Label RCT of 10 Days or 5 Days of Remdesivir Compared With Standard of Care in Hospitalized Patients With Moderate COVID-19[4]		

Key Inclusion Criteria:
• Laboratory-confirmed SARS-CoV-2 infection
• Pulmonary infiltrates
• SpO_2 >94% on room air
Key Exclusion Criteria:
• ALT or AST >5 times ULN
• CrCl <50 mL/min
Interventions:
• RDV 200 mg IV on Day 1, then RDV 100 mg daily for 9 days (n = 193)
• RDV 200 mg IV on Day 1, then RDV 100 mg daily for 4 days (n = 191)
• Local SOC (n = 200)
Primary Endpoint:
• Clinical status at Day 11, as measured by an OS
	Participant Characteristics:
	• Demographic and baseline disease characteristics similar across arms
	• Ranges for participant characteristics across the 3 arms:
	  • Median age 56–58 years
	  • Men: 60% to 63%
	  • 81% to 87% required no supplemental oxygen; 12% to 18% required low-flow oxygen; 1% required high-flow oxygen or NIV
	• Concomitant medication use in the 10-day RDV, 5-day RDV, and SOC arms:
	  • Steroids: 15%, 17%, 19%
	  • Tocilizumab: 1%, 1%, 5%
	  • HCQ/CQ: 11%, 8%, 45%
	  • LPV/RTV: 6%, 5%, 22%
	  • AZM: 21%, 18%, 31%
	• Median length of therapy: 6 days in 10-day RDV arm; 5 days in 5-day RDV arm
	Primary Outcomes:
	• Clinical status at Day 11:
	  • Significantly better in 5-day RDV arm than in SOC arm (OR 1.65; 95% CI, 1.09–2.48; $P = 0.02$)
	  • No difference in clinical status at Day 11 between 10-day RDV arm and SOC arm ($P = 0.18$)
		Key Limitations:
		• Open-label design may have affected decisions on concomitant medications (e.g., more patients in the SOC arm received AZM, HCQ or CQ, and LPV/RTV) and time of hospital discharge.
		• 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 clinical status at Day 11 than those who received SOC.
		• There was no difference in the clinical status at Day 11 between patients who received 10 days of RDV and those who received SOC.

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Methods	Results	Limitations and Interpretation
GS-US-540-5773 Study: Multinational, Open-Label RCT of 10 Days or 5 Days of Remdesivir Compared with Standard of Care in Hospitalized Patients With Moderate COVID-19[5]		

Key Inclusion Criteria:
• Laboratory-confirmed SARS-CoV-2 infection
• Pulmonary infiltrates and SpO_2 ≤94% on room air or receipt of supplemental oxygen
Key Exclusion Criteria:
• Need for MV or ECMO
• Multiorgan failure
• ALT or AST >5 times ULN
• Estimated CrCl <50 mL/min
Interventions:
• RDV 200 mg IV on Day 1, then RDV 100 mg daily for 4 days (n = 200)
• RDV 200 mg IV on Day 1, then RDV 100 mg daily for 9 days (n = 197)
Primary Endpoint:
• Clinical status at Day 14, as measured by an OS
Key Secondary Endpoints:
• Time to clinical improvement
• Time to recovery
	Participant Characteristics:
	• Median age 61 years in 5-day arm; 62 years in 10-day arm
	• 60% men in 5-day arm; 68% men in 10-day arm
	• Oxygen requirements at baseline for the 5-day and 10-day arms:
	  • None: 17%, 11%
	  • Low-flow supplemental oxygen: 56%, 54%
	  • High-flow oxygen or NIV: 24%, 30%
	  • MV or ECMO: 2%, 5%
	• Baseline clinical status: worse in 10-day arm than in 5-day arm ($P = 0.02$)
	Primary Outcome:
	• Day 14 distribution in clinical status after adjusting for baseline clinical status: similar between arms ($P = 0.14$)
	Secondary Outcomes:
	• Time to clinical improvement: similar between arms (10 days in 5-day arm vs. 11 days in 10-day arm)
	• Time to recovery: Median hospitalization duration for patients discharged on or before Day 14: similar between arms (7 days in 5-day arm vs. 8 days in 10-day arm)
		Key Limitations:
		• Open-label trial
		• Baseline imbalances in clinical status of patients in 5-day and 10-day arms
		Interpretation:
		• In hospitalized patients with severe COVID-19 who were not receiving MV or ECMO, using RDV for 5 or 10 days had similar clinical benefits.

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Methods	Results	Limitations and Interpretation
PINETREE: Double-Blind, Placebo-Controlled RCT of Remdesivir for 3 Days in Nonhospitalized Patients With COVID-19 at High Risk for Disease Progression[6]		
Key Inclusion Criteria: • Laboratory-confirmed SARS-CoV-2 infection ≤4 days from screening • Aged ≥12 years • ≥1 risk factor for disease progression • Symptom onset ≤7 days from randomization • ≥1 ongoing COVID-19 symptom **Key Exclusion Criteria:** • COVID-19 vaccination • Supplemental oxygen • Previous hospitalization or treatment for COVID-19 **Interventions:** • RDV 200 mg IV on Day 1, then RDV 100 mg daily on Days 2 and 3 (n = 279) • Placebo (n = 283) **Primary Endpoints:** • COVID-19-related hospitalizations or death from any cause by Day 28 • Any AE **Key Secondary Endpoints:** • COVID-19-related, medically attended visit or death from any cause by Day 28	**Participant Characteristics:** • Mean age 50 years; 30.2% aged ≥60 years; 52.1% men • 80.4% White, 7.5% Black, 41.8% Hispanic/Latinx • 61.6% with DM; 55.2% with obesity; 47.4% with HTN • Median duration of symptoms before first infusion: 5 days (IQR 3–6 days) • Median time from RT-PCR confirmation: 2 days (IQR 1–4 days) **Primary Outcomes:** • COVID-19-related hospitalization or death from any cause by Day 28: 2 (0.7%) in RDV arm vs. 15 (5.3%) in placebo arm (HR 0.13; 95% CI, 0.03–0.59; *P* = 0.008) • AEs: 42.3% in RDV arm vs. 46.3% in placebo arm **Secondary Outcome:** • COVID-19-related medically attended visit or death from any cause by Day 28: 4 (1.6%) in RDV arm vs. 2 (8.3%) in placebo arm (HR 0.19; 95% CI, 0.07–0.56)	**Key Limitations:** • Study halted early due to administrative issues. • Vaccinated individuals were excluded. **Interpretation:** • Three consecutive days of IV RDV resulted in an 87% relative reduction in the risk of hospitalization or death when compared to placebo.

Key: AE: adverse event; ALT = alanine transaminase; AST = aspartate aminotransferase; AZM = azithromycin; CQ = chloroquine; CrCl = creatinine clearance; DM = diabetes mellitus; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; HCQ = hydroxychloroquine; HTN = hypertension; IV = intravenous; LPV/RTV = lopinavir/ritonavir; MV = mechanical ventilation; NIV = noninvasive ventilation; OS = ordinal scale; the Panel = the COVID-19 Treatment Guidelines Panel; RCT = randomized controlled trial; RDV = remdesivir; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SOC = standard of care; SpO_2 = oxygen saturation; ULN = upper limit of normal; WHO = World Health Organization

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Ritonavir-Boosted Nirmatrelvir (Paxlovid)

Last Updated: May 13, 2022

Nirmatrelvir is an orally bioavailable protease inhibitor that is active against M^{PRO}, a viral protease that plays an essential role in viral replication by cleaving the 2 viral polyproteins.[1] It has demonstrated antiviral activity against all coronaviruses that are known to infect humans.[2] Nirmatrelvir is packaged with ritonavir (as Paxlovid), a strong cytochrome P450 (CYP) 3A4 inhibitor and pharmacokinetic boosting agent that has been used to boost HIV protease inhibitors. Coadministration of ritonavir is required to increase nirmatrelvir concentrations to the target therapeutic range. The Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for ritonavir-boosted nirmatrelvir on December 22, 2021, for the treatment of COVID-19.[3]

Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using **nirmatrelvir 300 mg with ritonavir 100 mg (Paxlovid)** orally (PO) twice daily for 5 days in nonhospitalized adults and pediatric patients aged ≥12 years and weighing ≥40 kg with mild to moderate COVID-19 who are at high risk of disease progression;[4] treatment should be initiated as soon as possible and within 5 days of symptom onset **(AIIa)**.

Ritonavir-boosted nirmatrelvir has significant drug-drug interactions, primarily due to the ritonavir component of the combination. Before prescribing ritonavir-boosted nirmatrelvir, **clinicians should carefully review the patient's concomitant medications**, including over-the-counter medications, herbal supplements, and recreational drugs, to evaluate potential drug-drug interactions.

The following resources provide information on identifying and managing drug-drug interactions.

- Quick reference lists:
  - Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications. Box 1 lists commonly prescribed outpatient medications that are not expected to have clinically relevant interactions with ritonavir-boosted nirmatrelvir, and Box 2 lists medications that have clinically relevant drug-drug interactions with ritonavir-boosted nirmatrelvir.
- Web-based drug-drug interaction checker:
  - The Liverpool COVID-19 Drug Interactions website
- Tables with guidance on managing specific drug-drug interactions:
  - The Ontario COVID-19 Science Advisory Table
  - The FDA EUA fact sheet and checklist for ritonavir-boosted nirmatrelvir

For the Panel's recommendations on preferred and alternative antiviral therapies for outpatients with COVID-19, see Therapeutic Management of Nonhospitalized Adults With COVID-19.

Rationale

The EPIC-HR trial demonstrated that starting ritonavir-boosted nirmatrelvir treatment in nonhospitalized adults with mild to moderate COVID-19 within 5 days of symptom onset reduced the risk of hospitalization or death through Day 28 by 89% compared to placebo.[3,5] This efficacy is comparable to remdesivir (87% relative reduction)[6] and greater than the efficacy reported for molnupiravir (30% relative reduction).[7]

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Ritonavir-boosted nirmatrelvir is expected to be active against the Omicron (B.1.1.529) variant and its BA.2 subvariant,[8] although there is currently a lack of data on the clinical efficacy of ritonavir-boosted nirmatrelvir against this variant and subvariant.[9-11] Because of the potential for significant drug-drug interactions with concomitant medications, this regimen may not be the optimal choice for all patients (see Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir [Paxlovid] and Concomitant Medications).

Clinical Data

The EPIC-HR study was a multinational randomized trial that compared ritonavir-boosted nirmatrelvir PO twice daily for 5 days to placebo in nonhospitalized patients aged ≥18 years with mild to moderate COVID-19 who were at high risk of clinical progression. Eligible patients were randomized within 5 days of symptom onset, were unvaccinated against COVID-19, and had at least 1 risk factor for progression to severe disease.[5] Patients were excluded if they used medications that were either highly dependent upon CYP3A4 for clearance or strong inducers of CYP3A4.

A total of 2,246 patients enrolled in the trial. The mean age was 46 years, 51% of the patients were men, and 72% were White. Forty-seven percent of the patients tested negative for SARS-CoV-2 antibodies, and 66% started study treatment within 3 days of symptom onset.

Patients who were randomized within 3 days of symptom onset (n = 1,379) were included in the modified intention-to-treat (mITT) analysis. COVID-19-related hospitalizations or all-cause deaths occurred by Day 28 in 5 of 697 patients (0.72%) in the ritonavir-boosted nirmatrelvir arm and in 44 of 682 patients (6.5%) in the placebo arm. Among the 2,085 patients who were randomized within 5 days of symptom onset (mITT1 analysis), COVID-19-related hospitalizations and all-cause deaths occurred in 8 of 1,039 patients (0.77%) in the ritonavir-boosted nirmatrelvir arm and in 66 of 1,046 patients (6.3%) in the placebo arm (89% relative risk reduction; -5.6% estimated absolute reduction; 95% CI, -7.2% to -4.0%; $P < 0.001$). There were no deaths in the ritonavir-boosted nirmatrelvir arm and 13 deaths in the placebo arm.

A total of 2,224 patients who received at least 1 dose of either ritonavir-boosted nirmatrelvir or placebo were included in the EPIC-HR safety analysis set. Among these patients, dysgeusia and diarrhea occurred more frequently in ritonavir-boosted nirmatrelvir recipients than in placebo recipients (6% vs. 0.3% and 3% vs. 2%, respectively). Fewer ritonavir-boosted nirmatrelvir recipients discontinued the study drug due to an adverse event than placebo recipients (2% vs. 4%).

Additional Considerations

- Nirmatrelvir must be administered with ritonavir to achieve sufficient therapeutic plasma concentrations.
- Patients should complete the 5-day treatment course of ritonavir-boosted nirmatrelvir. It is unknown whether a shorter course is less effective or associated with the emergence of nirmatrelvir-resistant mutations.
- If a patient requires hospitalization after starting treatment, the full treatment course of ritonavir-boosted nirmatrelvir can be completed at the clinician's discretion.
- Ritonavir-boosted nirmatrelvir may be used in patients who are hospitalized for a diagnosis other than COVID-19, provided they have mild to moderate COVID-19, are at high risk of progressing to severe disease, and are within 5 days of symptom onset.
- There are no data on using combinations of antiviral therapies or combinations of antiviral agents and anti-SARS-CoV-2 monoclonal antibodies for the treatment of nonhospitalized patients with

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COVID-19. Clinical trials are needed to determine whether combination therapy has a role in the treatment of COVID-19.

- Severely immunocompromised patients can experience prolonged periods of SARS-CoV-2 replication, which may lead to rapid viral evolution. There are theoretical concerns that using a single antiviral agent in these patients may produce antiviral-resistant viruses. Additional studies are needed to assess this risk. The role of combination antiviral therapy or a longer treatment duration in treating severely immunocompromised patients is not yet known.
- Case reports have described SARS-CoV-2 viral rebound and the recurrence of COVID-19 symptoms in some patients who have completed treatment with ritonavir-boosted nirmatrelvir. Case reports and results from the EPIC-HR trial also describe instances of increases in SARS-CoV-2 RNA levels following completion of the treatment course.[12,13] The frequency, mechanism, and clinical implications of these events are not yet known. There are currently no data on the efficacy of administering longer courses or a second course of ritonavir-boosted nirmatrelvir.

Monitoring and Adverse Effects

The most common adverse effects of ritonavir-boosted nirmatrelvir are dysgeusia, diarrhea, hypertension, and myalgia.

Renal impairment reduces the clearance of nirmatrelvir. In patients with suspected renal impairment, clinicians may consider checking the patient's renal function to inform the dosing of ritonavir-boosted nirmatrelvir. The dose should be reduced to nirmatrelvir 150 mg with ritonavir 100 mg twice daily in patients with moderate renal impairment (i.e., those with an estimated glomerular filtration rate [eGFR] of ≥30 to <60 mL/min). Ritonavir-boosted nirmatrelvir **is not recommended** in patients with an eGFR of <30 mL/min until more data are available. The appropriate dose for patients with severe renal impairment has not been determined.

Ritonavir-boosted nirmatrelvir **is not recommended** for patients with known or suspected severe hepatic impairment (i.e., Child-Pugh Class C), and it should be used with caution in patients with pre-existing liver diseases, liver enzyme abnormalities, or hepatitis. No pharmacokinetic or safety data are available for this patient population.

Considerations in Pregnancy

Pregnancy is a risk factor for severe COVID-19.[4] However, like many clinical trials of treatments for COVID-19, the EPIC-HR trial excluded pregnant and lactating individuals. Ritonavir has been used extensively during pregnancy in people with HIV and has a documented safety profile during pregnancy. The mechanisms of action for both nirmatrelvir and ritonavir and the results of animal studies of ritonavir-boosted nirmatrelvir suggest that this regimen can be used safely in pregnant individuals. Ritonavir-boosted nirmatrelvir should be offered to pregnant and recently pregnant patients with COVID-19 who qualify for this therapy based on the results of a risk-benefit assessment. The risk-benefit assessment for using ritonavir-boosted nirmatrelvir in pregnant patients may include factors such as medical comorbidities, body mass index, and vaccination status. Obstetricians should be aware of potential drug-drug interactions when prescribing this agent.

Considerations in Children

Ritonavir-boosted nirmatrelvir is authorized for use in pediatric patients aged ≥12 years and weighing ≥40 kg. The EPIC-HR trial excluded persons aged <18 years. The safety and efficacy of using ritonavir-boosted nirmatrelvir in pediatric patients has not been established in clinical trials.

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Drug-Drug Interactions

Ritonavir-boosted nirmatrelvir has significant drug-drug interactions, primarily due to the ritonavir component of the combination. Boosting with ritonavir, which is a strong CYP3A inhibitor and a P-glycoprotein inhibitor, is required to increase the exposure of nirmatrelvir to a concentration that is effective against SARS-CoV-2. However, it may also increase concentrations of certain concomitant medications, thereby increasing the potential for serious and sometimes life-threatening drug toxicities. Additionally, ritonavir is an inhibitor, inducer, and substrate of various other drug-metabolizing enzymes and/or drug transporters.

Because ritonavir-boosted nirmatrelvir is the only highly effective oral antiviral for the treatment of COVID-19, **drug-drug interactions that can be safely managed should not preclude the use of this medication**.

The treatment course of ritonavir-boosted nirmatrelvir for COVID-19 is 5 days. CYP3A4 inhibition occurs rapidly after initiating ritonavir, with maximum inhibition occurring within 48 hours.[14] After ritonavir is discontinued, 70% to 90% of CYP3A4 inhibition resolves within 2 to 3 days.[15] The time to resolution of inhibition varies based on factors such as the patient's age; therefore, resolution may take longer in some individuals, such as in the elderly. When ritonavir is used for 5 days, its induction properties are less likely to be clinically relevant than when the drug is used chronically (e.g., in people who take HIV protease inhibitors).[16] Both nirmatrelvir and ritonavir are substrates of CYP3A. Thus, ritonavir-boosted nirmatrelvir should not be given within 2 weeks of administering a strong CYP3A4 inducer (e.g., St. John's wort, rifampin). Ritonavir-boosted nirmatrelvir is **contraindicated** in this setting, as the delayed offset of enzyme induction can reduce the concentrations of nirmatrelvir and ritonavir, which may render the treatment ineffective against SARS-CoV-2. An alternative treatment for COVID-19 should be prescribed instead.

See Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications for guidance on managing potential drug-drug interactions.

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Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications

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Ritonavir, a strong cytochrome P450 (CYP) 3A4 inhibitor and a P-glycoprotein inhibitor, is coadministered with nirmatrelvir to increase the blood concentration of nirmatrelvir, thereby making it effective against SARS-CoV-2. Ritonavir may also increase blood concentrations of certain concomitant medications. Because ritonavir-boosted nirmatrelvir (Paxlovid) is the only highly effective oral antiviral for the treatment of COVID-19, drug interactions that can be safely managed should not preclude the use of this medication.

Clinicians should be aware that many commonly used medications can be safely coadministered with ritonavir-boosted nirmatrelvir despite its drug-drug interaction potential. Box 1 includes commonly prescribed medications that are not expected to have clinically relevant interactions with ritonavir-boosted nirmatrelvir.

Box 1. Commonly Prescribed Outpatient Medications Not Expected to Have Clinically Relevant Interactions With Ritonavir-Boosted Nirmatrelvir (Paxlovid)

Medications Without Clinically Relevant Interactions		
These commonly prescribed medications may be coadministered without dose adjustment and without increased monitoring.[a] This list is not inclusive of all noninteracting medications within each drug category.		
Acid reducing agents • Famotidine • Omeprazole • Pantoprazole **Allergy medications** • Cetirizine • Diphenhydramine • Loratadine **Anti-infective agents** • Azithromycin • Hydroxychloroquine **Cardiovascular agents** • Aspirin • Atenolol • Carvedilol • Furosemide • Hydrochlorothiazide • Irbesartan • Isosorbide Dinitrate • Lisinopril • Losartan • Metoprolol • Prasugrel	**Diabetes medications** • Empagliflozin • Insulin • Metformin • Pioglitazone **Immunosuppressants** • Methotrexate • Mycophenolate • Prednisone **Lipid-modifying agents** • Ezetimibe • Pitavastatin • Pravastatin **Neuropsychiatric agents** • Amitriptyline • Bupropion • Citalopram • Duloxetine • Escitalopram • Fluoxetine • Gabapentin • Lorazepam • Nortriptyline • Olanzapine • Paroxetine • Sertraline • Venlafaxine	**Pain medications** • Acetaminophen • Aspirin • Codeine • Ibuprofen • Naproxen **Respiratory medications** • Corticosteroids (inhaled) • Formoterol • Montelukast **Miscellaneous** • Allopurinol • Contraceptives (oral)[b] • Donepezil • Enoxaparin • Finasteride • Levothyroxine • Ondansetron

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Medications Without Clinically Relevant Interactions, continued
[a] This list is primarily based on the most common medication searches by U.S. users on the Liverpool COVID-19 Drug Interactions website between January 1 and April 13, 2022 (internal communication, April 2022). The Liverpool website classifies these medications as those that have no interaction or weak interaction with ritonavir-boosted nirmatrelvir.
[b] The Food and Drug Administration Emergency Use Authorization for ritonavir-boosted nirmatrelvir suggests that individuals who use contraceptive products containing ethinyl estradiol consider using a backup, nonhormonal contraceptive method because coadministration may result in low ethinyl estradiol levels. However, the low level is not expected to be clinically significant during 5 days of therapy. The progestin concentration of a combined hormonal contraceptive is expected to remain similar or increase with coadministration, which would maintain the effectiveness of the oral contraceptive.

Medications That Have Clinically Relevant Drug-Drug Interactions With Ritonavir-Boosted Nirmatrelvir

Clinicians should be aware that, in some cases, drug-drug interactions with ritonavir-boosted nirmatrelvir may lead to serious or life-threatening drug toxicities. The recommended treatment course of ritonavir-boosted nirmatrelvir for COVID-19 is 5 days. After the last dose is administered, most of the interaction potential resolves within 2 to 3 days, although resolution may take longer in elderly adults.[1]

Ritonavir-boosted nirmatrelvir should not be given within 2 weeks of administering a strong CYP3A4 inducer (e.g., St. John's wort, rifampin). Ritonavir-boosted nirmatrelvir is **contraindicated** in this setting, because strong CYP3A4 inducers may reduce the concentrations of nirmatrelvir and ritonavir, rendering the treatment ineffective against SARS-CoV-2. Alternative treatment for COVID-19 should be prescribed.

Identifying Drug-Drug Interactions

Before prescribing ritonavir-boosted nirmatrelvir, carefully review the patient's concomitant medications, including over-the-counter medicines, herbal supplements, and recreational drugs.

Consult 1 or more of the following resources for information on identifying and managing drug-drug interactions:

- Quick reference lists:
  - Box 1 lists commonly prescribed outpatient medications that are not expected to have clinically relevant interactions with ritonavir-boosted nirmatrelvir.
  - Box 2 lists medications that have clinically relevant drug-drug interactions with ritonavir-boosted nirmatrelvir.
- Web-based drug-drug interaction checker:
  - The Liverpool COVID-19 Drug Interactions website
- Tables with guidance on managing specific drug-drug interactions:
  - The Ontario COVID-19 Science Advisory Table
  - The Food and Drug Administration Emergency Use Authorization fact sheet and checklist for ritonavir-boosted nirmatrelvir

Consider expert consultation (e.g., with a pharmacist, an HIV specialist, or the patient's specialist providers), especially for patients receiving highly specialized therapies or drugs prone to concentration-dependent toxicities, such as certain anticonvulsant, anticoagulant, antiarrhythmic, chemotherapeutic, neuropsychiatric, and immunosuppressant drugs.

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Management Strategies for Drug-Drug Interactions

Consider the magnitude and significance of the potential interaction when choosing management strategies for patients who are to receive ritonavir-boosted nirmatrelvir. Potential strategies include:

- Temporarily withholding the concomitant medication,
- Increasing monitoring for potential adverse reactions to the concomitant medication,
- Adjusting the dose of the concomitant medication,
- Using an alternative to the concomitant medication, *or*
- Using alternative COVID-19 therapies (see Therapeutic Management of Nonhospitalized Adults With COVID-19).

Use the chosen strategy for the 5-day duration of ritonavir-boosted nirmatrelvir treatment and for at least 2 to 3 days after treatment completion. The strategy may need to continue for a longer duration if ritonavir-boosted nirmatrelvir is initiated in an elderly patient or if the interacting medication has a long half-life.

Box 2. Outpatient Medications That Have Clinically Relevant Drug-Drug Interactions With Ritonavir-Boosted Nirmatrelvir (Paxlovid)

Not all medications that may interact with ritonavir-boosted nirmatrelvir are included in Box 2. Deviation from the recommended strategies may be appropriate in certain clinical scenarios.

Prescribe Alternative COVID-19 Therapy		
For these medications, management strategies are not possible or feasible, or the risks outweigh the potential benefits.		
Anticonvulsants • Carbamazepine • Phenobarbital • Phenytoin • Primidone **Anti-infective agents** • Glecaprevir/pibrentasvir • Rifampin • Rifapentine **Immunosuppressants** • Voclosporin	**Cardiovascular agents** • Amiodarone • Clopidogrel[a,b] • Disopyramide • Dofetilide • Dronedarone • Eplerenone • Flecainide • Ivabradine • Propafenone • Quinidine **Neuropsychiatric agents** • Clozapine • Lumateperone • Lurasidone • Midazolam (oral) • Pimozide	**Pain medications** • Meperidine (pethidine) **Pulmonary hypertension medications** • Sildenafil • Tadalafil • Vardenafil **Miscellaneous** • Bosentan • Certain chemotherapeutic agents[c] • Ergot derivatives • Lumacaftor/ivacaftor • St. John's wort • Tolvaptan

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Temporarily Withhold Concomitant Medication, If Clinically Appropriate		
Withhold these medications during ritonavir-boosted nirmatrelvir treatment and for at least 2–3 days after treatment completion. They may need to be withheld for longer if the patient is elderly or the medication has a long half-life. If withholding is not clinically appropriate, use an alternative concomitant medication or COVID-19 therapy.		
Anticoagulants • Rivaroxaban[d] **Anti-infective agents** • Erythromycin **BPH medications** • Alfuzosin • Silodosin **Cardiovascular agents** • Aliskiren • Ranolazine • Ticagrelor[b] • Vorapaxar **Immunosuppressants[f]** • Everolimus • Sirolimus • Tacrolimus	**Lipid-modifying agents** • Atorvastatin[e] • Lomitapide • Lovastatin[e] • Rosuvastatin[e] • Simvastatin[e] **Migraine medications** • Eletriptan • Rimegepant • Ubrogepant **Neuropsychiatric agents** • Clonazepam[g] • Clorazepate[g] • Diazepam[g] • Estazolam[g] • Flurazepam[g] • Suvorexant • Triazolam[g]	**Erectile dysfunction medications** • Avanafil **Respiratory medications** • Salmeterol **Miscellaneous** • Certain chemotherapeutic agents[c] • Colchicine[h] • Finerenone • Flibanserin • Naloxegol

Adjust Concomitant Medication Dose and Monitor for Adverse Effects		
Consult the Liverpool COVID-19 Drug Interactions website or the Ontario COVID-19 Science Advisory Table for specific dosing recommendations.[i] If the dose of the concomitant medication cannot be adjusted, withhold the medication (if clinically appropriate) or use an alternative concomitant medication or COVID-19 therapy.		
Anticoagulants • Apixaban • Dabigatran • Edoxaban **Anti-infective agents** • Clarithromycin • Itraconazole • Ketoconazole • Maraviroc • Rifabutin **BPH medications** • Tamsulosin **Cardiovascular agents** • Cilostazol • Digoxin • Mexiletine **Diabetes medications** • Saxagliptin	**Erectile dysfunction medications** • Sildenafil • Tadalafil • Vardenafil **Immunosuppressants[f]** • Cyclosporine **Neuropsychiatric agents** • Alprazolam[g] • Aripiprazole • Brexpiprazole • Buspirone • Cariprazine • Chlordiazepoxide[g] • Clobazam[g] • Iloperidone • Pimavanserin • Quetiapine • Trazodone	**Pain medications** • Fentanyl • Hydrocodone • Oxycodone **Pulmonary hypertension medications** • Riociguat **Miscellaneous** • Certain chemotherapeutic agents[c] • Darifenacin • Elexacaftor/tezacaftor/ivacaftor • Eluxadoline • Ivacaftor • Tezacaftor/ivacaftor

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Continue Concomitant Medication and Monitor for Adverse Effects		
Pre-emptive dose adjustment is not required but may be considered. Educate patients on potential adverse effects. Consult the Liverpool COVID-19 Drug Interactions website or the Ontario COVID-19 Science Advisory Table for monitoring guidance and dose adjustment information if needed.[i]		
Anticoagulants • Warfarin **Anti-infective agents** • Cobicistat or ritonavir-boosted antiretrovirals • Isavuconazole • Posaconazole • Voriconazole **BPH medications** • Doxazosin • Terazosin **Diabetes medications** • Glyburide	**Cardiovascular agents** • Amlodipine • Diltiazem • Felodipine • Nifedipine • Sacubitril • Valsartan • Verapamil **Neuropsychiatric agents** • Haloperidol • Hydroxyzine • Mirtazapine • Risperidone • Ziprasidone • Zolpidem	**Pain medications** • Buprenorphine • Hydromorphone • Methadone • Morphine • Tramadol

[a] Reduced effectiveness of clopidogrel is likely. It may be acceptable to continue clopidogrel if the benefit of ritonavir-boosted nirmatrelvir treatment outweighs the risk of reduced clopidogrel effectiveness.

[b] For patients at very high risk of thrombosis (e.g., received a coronary stent within the past 6 weeks), consider prescribing an alternative antiplatelet (e.g., prasugrel) or an alternative COVID-19 therapy.

[c] Ritonavir-boosted nirmatrelvir may increase concentrations of some chemotherapeutic agents, leading to an increased potential for drug toxicities. Some chemotherapeutic agents may decrease the effectiveness of ritonavir-boosted nirmatrelvir. Please refer to the FDA EUA ritonavir-boosted nirmatrelvir fact sheet and the prescribing information for the chemotherapeutic agent and consult the patient's specialist provider. The University Health Network/Kingston Health Sciences Centre is an additional resource for evaluating drug-drug interactions for chemotherapeutic agents.

[d] For patients at high risk of arterial or venous thrombosis (e.g., had a stroke within the past 3 months with a CHA_2DS_2-VASc score of 7–9 or a pulmonary embolism within the past month), consult the primary or specialty provider and consider using an alternative anticoagulant or COVID-19 therapy.

[e] For lovastatin and simvastatin, withhold at least 12 hours before initiation of ritonavir-boosted nirmatrelvir, during treatment, and for 5 days after treatment completion. For atorvastatin and rosuvastatin, withhold at the beginning of treatment with ritonavir-boosted nirmatrelvir and resume after completion of the 5-day course. If withholding a statin is not clinically appropriate (e.g., the patient had a recent myocardial infarction), the doses of atorvastatin and rosuvastatin can be adjusted and continued, and lovastatin and simvastatin should be switched to an alternative statin.

[f] Consult a patient's specialist providers before coadministering these immunosuppressants and ritonavir-boosted nirmatrelvir. These immunosuppressants have significant drug-drug interaction potential with ritonavir, and close monitoring may not be feasible. Alternative COVID-19 therapy may need to be considered. See the American Society of Transplantation statement for more information.

[g] Abrupt discontinuation or rapid dose reduction of benzodiazepines may precipitate an acute withdrawal reaction.[2] The risk is greatest for patients who have been using high doses of benzodiazepines over an extended period.

[h] For patients with severe hepatic or renal impairment, coadministration of colchicine and ritonavir-boosted nirmatrelvir is **contraindicated** due to the potential for serious or life-threatening reactions.

[i] For medications not included on the Liverpool COVID-19 Drug Interactions website or the Ontario COVID-19 Science Advisory Table, refer to the medication's FDA label for information on coadministration with ritonavir or other strong CYP3A4 and/or P-gp inhibitors.

Key: BPH = benign prostatic hyperplasia; CHA_2DS_2-VASc = congestive heart failure, hypertension, age, diabetes, stroke, vascular disease; CYP = cytochrome P450; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; P-gp = P-glycoprotein

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Molnupiravir

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Molnupiravir is the oral prodrug of beta-D-N4-hydroxycytidine (NHC), a ribonucleoside that has broad antiviral activity against RNA viruses. NHC uptake by viral RNA-dependent RNA-polymerases results in viral mutations and lethal mutagenesis.[1,2]

On December 23, 2021, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for molnupiravir for the treatment of adults with mild to moderate COVID-19 who are within 5 days of symptom onset, who are at high risk of progressing to severe disease, and for whom alternative antiviral therapies are not accessible or clinically appropriate.[3,4]

Molnupiravir has potent antiviral activity against SARS-CoV-2.[1,5] As a mutagenic ribonucleoside antiviral agent, there is a theoretical risk that molnupiravir will be metabolized by the human host cell and incorporated into the host DNA, leading to mutations. Molnupiravir has been evaluated in 2 in vivo rodent mutagenicity assays. One study produced equivocal results; in the other study, there was no evidence for mutagenicity.[4] The FDA concluded that, based on the available genotoxicity data and the 5-day duration of treatment, molnupiravir has a low risk for genotoxicity.[4] In addition, there have been concerns about the potential effects of molnupiravir on SARS-CoV-2 mutation rates; the FDA is requiring the manufacturer to establish a process to monitor genomic databases for the emergence of SARS-CoV-2 variants.

Recommendations

- In nonhospitalized patients aged ≥18 years who have mild to moderate COVID-19 and who are at high risk of disease progression, the COVID-19 Treatment Guidelines Panel (the Panel) recommends using **molnupiravir** 800 mg orally (PO) twice daily for 5 days **ONLY** when ritonavir-boosted nirmatrelvir (Paxlovid) or remdesivir cannot be used; treatment should be initiated as soon as possible and within 5 days of symptom onset **(CIIa)**.
- The FDA EUA states that molnupiravir is not recommended for use in pregnant patients because fetal toxicity has been reported in animal studies of molnupiravir. However, when other therapies are not available, pregnant people with COVID-19 who are at high risk of progressing to severe disease may reasonably choose molnupiravir therapy after being fully informed of the risks, particularly if they are beyond the time of embryogenesis (i.e., >10 weeks' gestation). The prescribing clinician should document that a discussion of the risks and benefits occurred and that the patient chose this therapy.
- People who engage in sexual activity that may result in conception should use effective contraception during and following treatment with molnupiravir. For more details, see the Considerations in Sexually Active Individuals section below.
- There are no data on the use of molnupiravir in patients who have received COVID-19 vaccines. The risk-to-benefit ratio is likely to be less favorable in these patients, because molnupiravir has a lower efficacy compared to other available treatments.

For the Panel's recommendations on using antiviral therapies in outpatients and prioritizing outpatient therapies when there are logistical or supply constraints, see Therapeutic Management of Nonhospitalized Adults With COVID-19.

Rationale

In the MOVe-OUT trial, molnupiravir reduced the rate of hospitalization or death by 30% compared to

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placebo.[4] Even though the different treatment options have not been directly compared in clinical trials, the Panel recommends using molnupiravir only when ritonavir-boosted nirmatrelvir and remdesivir are not available or cannot be given, because molnupiravir has lower efficacy than the other options. For more information, see Therapeutic Management of Nonhospitalized Adults With COVID-19.

Molnupiravir is expected to be active against the B.1.1.529 (Omicron) variant of concern, although in vitro and in vivo data are currently limited.[6]

Additional Considerations

- Patients should complete the 5-day treatment course of molnupiravir. It is unknown whether a shorter course is less effective or associated with the emergence of molnupiravir-resistant mutations.
- If a patient requires hospitalization after starting treatment, the full treatment course of molnupiravir can be completed at the health care provider's discretion.
- Molnupiravir may be used in patients who are hospitalized for a diagnosis other than COVID-19, provided they have mild to moderate COVID-19 and are at high risk of progressing to severe disease.
- There are no data on using combination antiviral therapies or combinations of antiviral agents and anti-SARS-CoV-2 monoclonal antibodies for the treatment of nonhospitalized patients with COVID-19. Clinical trials are needed to determine whether combination therapy has a role in the treatment of SARS-CoV-2 infection.
- Severely immunocompromised patients can experience prolonged periods of SARS-CoV-2 replication, which may lead to rapid viral evolution. There are theoretical concerns that using a single antiviral agent in these patients may produce antiviral-resistant viruses. Additional studies are needed to assess this risk. The role of combination antiviral therapy in treating severely immunocompromised patients is not yet known.

Considerations in Sexually Active Individuals

Clinicians should assess a patient's pregnancy status before initiating molnupiravir, if clinically indicated.

Patients of childbearing potential should be counseled about abstaining from sex or using reliable contraception for the duration of therapy and for up to 4 days after receiving molnupiravir. Reproductive toxicity has been reported in animal studies of molnupiravir, and molnupiravir may be mutagenic during pregnancy.

The FDA EUA states that men of reproductive potential who are sexually active with individuals of childbearing potential should be counseled to abstain from sex or use a reliable method of contraception for the duration of treatment **and for at least 3 months after the last dose of molnupiravir**.

Considerations in Pregnancy

The FDA EUA states that molnupiravir is not recommended for use in pregnant patients because fetal toxicity has been reported in animal studies of molnupiravir. However, when other therapies are not available, pregnant people with COVID-19 who are at high risk of progressing to severe disease may reasonably choose molnupiravir therapy after being fully informed of the risks, particularly if they are beyond the time of embryogenesis (i.e., >10 weeks' gestation). The prescribing clinician should document that a discussion of the risks and benefits occurred, and that the patient chose this therapy. The patient should also be informed about the pregnancy surveillance program and offered the opportunity to

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participate.

There is currently a lack of data on the use of molnupiravir in lactating people, and molnupiravir may cause adverse effects in infants who are exposed to the drug through breastfeeding. Because of this, the FDA EUA states that lactating people should not breastfeed their infants during treatment with molnupiravir and for 4 days after the final dose. Pumping and discarding breast milk to maintain supply during this time is recommended.

Considerations in Children

The MOVe-OUT trial excluded participants aged <18 years. There are no data available on the use of molnupiravir in children aged <18 years. Molnupiravir is not authorized for use in children aged <18 years due to potential effects on bone and cartilage growth.

Monitoring, Adverse Effects, and Drug Interactions

The most common adverse effects of molnupiravir are diarrhea, nausea, and dizziness. Based on in vitro studies, neither molnupiravir nor its active metabolite NHC are inhibitors or inducers of major drug-metabolizing enzymes or inhibitors of major drug transporters. According to the EUA, no drug-drug interactions have been identified for molnupiravir.

Clinical Trial Data

MOVe-OUT was a multinational, Phase 3 trial that evaluated the use of molnupiravir in nonhospitalized adults with mild to moderate COVID-19 who were at high risk of progressing to severe COVID-19. The participants were not pregnant, had not been vaccinated against COVID-19, and were enrolled within 5 days of symptom onset. They were randomized to receive molnupiravir 800 mg PO every 12 hours for 5 days or placebo.[7] The primary composite outcome was all-cause hospitalizations (defined as hospital stays that lasted >24 hours) and deaths by Day 29.

The final analysis included 1,433 participants; the median age was 43 years (with 17% aged >60 years). Forty-nine percent of the participants were men, 57% were White, 50% were Hispanic/Latinx, and 5% were Black or African American. Among the participants, 74% had a body mass index ≥30 and 16% had diabetes. The time from COVID-19 symptom onset to randomization was ≤3 days in 48% of participants.

By Day 29, hospitalizations or deaths had occurred in 48 of 709 participants (6.8%) in the molnupiravir arm and in 68 of 699 participants (9.7%) in the placebo arm (30% relative risk reduction; -3.0% adjusted difference; 95% CI, -5.9% to -0.1%; $P = 0.0218$).[4] There was 1 death in the molnupiravir arm and 9 deaths in the placebo arm. There were no significant differences between the arms in the proportion of participants who experienced adverse events or serious adverse events.

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Chloroquine or Hydroxychloroquine and/or 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 and rheumatoid arthritis, in addition to malaria.

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

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

Recommendation

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

Rationale

Hospitalized Patients

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

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

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

In addition to these randomized trials, data from large retrospective observational studies do not consistently show evidence of a benefit for hydroxychloroquine with or without azithromycin in hospitalized patients with COVID-19.[13-15] Please see Table 2b or the archived versions of the Guidelines for more information.

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

Nonhospitalized Patients

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

An open-label, prospective, randomized trial compared oral azithromycin 500 mg once daily for 3 days plus standard of care to standard of care alone in nonhospitalized, high-risk, older adults who had laboratory-confirmed or suspected COVID-19. No differences were observed between the arms in the primary endpoints of time to first self-reported recovery and hospitalization or death due to COVID-19. These findings remained consistent in an analysis that was restricted to participants with positive SARS-CoV-2 PCR results. The study was ultimately halted due to futility.[19] Similarly, in a preliminary report from ATOMIC-2, adding oral azithromycin 500 mg once daily to standard of care for 14 days did not reduce the risk of hospitalization or death among 292 participants with mild to moderate COVID-19.[20]

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

Adverse Effects

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

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

Drug-Drug Interactions

Chloroquine and hydroxychloroquine are moderate inhibitors of cytochrome P450 2D6, and these drugs

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are also P-glycoprotein inhibitors. Chloroquine and hydroxychloroquine may decrease the antiviral activity of remdesivir; coadministration of these drugs **is not recommended**.[25]

Drug Availability

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

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Table 2b. Chloroquine or Hydroxychloroquine and/or Azithromycin: Selected Clinical Data

Last Updated: July 8, 2021

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

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

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

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Study Design	Methods	Results	Limitations and Interpretation
Solidarity Trial: Hydroxychloroquine in Hospitalized Patients With COVID-19[20], continued			
	Primary Endpoint: • In-hospital mortality (i.e., death during the original hospitalization; follow-up ended at discharge from the hospital)	• Subgroup analyses based on age or respiratory support at entry reported no significant difference in mortality between the arms. • No difference between the arms in the secondary outcome of initiation of ventilation, and no difference in the composite outcome of in-hospital mortality or initiation of ventilation • The number of deaths due to any cardiac cause during the 14 days after enrollment (the dosing period) was lower in these 2 arms than in the other study arms (the RDV, LPV/RTV, and IFN arms and their respective control arms).	
PETAL Trial: Hydroxychloroquine in Hospitalized Patients With COVID-19[21]			
Randomized, placebo-controlled, blinded trial in hospitalized adults (n = 479)	**Key Inclusion Criteria:** • Laboratory-confirmed SARS-CoV-2 infection • Symptoms of respiratory illness for <10 days **Key Exclusion Criteria:** • More than 1 dose of HCQ or CQ during the previous 10 days • Prolonged QTc interval (>500 ms) **Interventions:** • HCQ 400 mg PO twice daily for 2 doses, then HCQ 200 mg PO twice daily for 8 doses • Matching placebo **Primary Endpoint:** • Clinical status 14 days after randomization, as measured by a 7-point ordinal scale (the COVID Outcomes Scale)	**Number of Participants:** • Enrollment occurred between April 2 and June 19, 2020. • HCQ (n = 242) and placebo (n = 237) • Planned sample size was 510 participants, but study enrollment was halted early due to futility. **Participant Characteristics:** • Median age was 58 and 57 years in HCQ and placebo arms, respectively; 33% of patients were aged ≥65 years and 24% of patients were Black/African American. • 33% to 36% of patients had diabetes mellitus, 6% to 12% had heart disease, and 7% to 9% had chronic lung disease. • At randomization, 5.4% of patients in HCQ arm and 8% in placebo arm were receiving IMV or ECMO. In both arms, 11% to 12% of patients were receiving noninvasive ventilation or HFNC oxygen, 46% to 48% were receiving low-flow oxygen, and 35% were receiving no respiratory support. • Among the patients who received concomitant medications, 22% received RDV, 19% received AZM, and 18% received corticosteroids. There was no difference in concomitant medication use between the arms.	**Key Limitations:** • It is unclear how the primary outcome of this study (a median COVID Outcomes Scale score) translates to clinical practice. **Interpretation:** • HCQ does not improve patient scores on the COVID Outcomes Scale in hospitalized patients with laboratory-confirmed SARS-CoV-2 infection when compared to placebo. • HCQ did not improve survival or time to discharge in these patients when compared to placebo.

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Study Design	Methods	Results	Limitations and Interpretation
PETAL Trial: Hydroxychloroquine in Hospitalized Patients With COVID-19[21], continued			
		Outcomes: • Median COVID Outcomes Scale score was 6 in HCQ arm (IQR 4–7) and 6 in placebo arm (IQR 4–7; aOR 1.02; 95% CI, 0.73–1.42). • No difference between the arms in the secondary outcome of all-cause, all-location death at Day 14 and Day 28 • No difference between the arms in the number of any of the following systematically collected safety events: cardiac arrest treated with CPR, symptomatic hypoglycemia, ventricular arrhythmia, or seizure • Among patients who had QTc assessed, 5.9% in HCQ arm and 3.3% in placebo arm had a recorded QTc interval >500 ms during the first 5 days of dosing.	
RECOVERY Trial[22]			
Open-label, randomized controlled platform trial with multiple arms; in 1 arm, hospitalized patients received HCQ (n = 11,197)	**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 IMV or ECMO, 60% were receiving oxygen only (with or without noninvasive ventilation), and 24% were receiving neither. • Use of AZM or another macrolide during the follow-up period was similar in both arms, as was use of dexamethasone.	**Key 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 IMV at the time of randomization were more likely to require intubation or die during hospitalization if they received HCQ.

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Study Design	Methods	Results	Limitations and Interpretation
RECOVERY Trial[22], continued			
		Outcomes: • No significant difference in 28-day mortality between the 2 arms; 421 patients (26.8%) in HCQ arm and 790 patients (27.0%) in SOC arm had died by Day 28 (rate ratio 1.09; 95% CI, 0.97–1.23; $P = 0.15$). • A similar 28-day mortality for HCQ patients was reported during the post hoc exploratory analysis that was restricted to the 4,266 participants (90.5%) who had a positive SARS-CoV-2 test result. • Patients in HCQ arm were less likely to survive hospitalization and had a longer median time to discharge than patients in SOC arm. • Patients who received HCQ and who were not on IMV at baseline had an increased risk of requiring intubation and an increased risk of death. • At the beginning of the study, the researchers did not record whether a patient developed a major cardiac arrhythmia after study enrollment; however, these data were later collected for 735 patients (47.1%) in HCQ arm and 1,421 patients (45.0%) in SOC arm. • No differences between the arms in the frequency of supraventricular tachycardia, ventricular tachycardia or fibrillation, or instances of AV block that required intervention; 1 case of Torsades de Pointes was reported in HCQ arm.	
Hydroxychloroquine and Hydroxychloroquine Plus Azithromycin for Mild or Moderate COVID-19[23]			
Open-label, 3-arm RCT in hospitalized adults (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:** • mITT analysis included patients with laboratory-confirmed SARS-CoV-2 infection (n = 504). **Participant Characteristics:** • Mean age was 50 years. • 58% of patients were men.	**Key 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

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Study Design	Methods	Results	Limitations and Interpretation
Hydroxychloroquine and Hydroxychloroquine Plus Azithromycin for Mild or Moderate COVID-19[23], 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 measured 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	• At baseline, 58.2% of patients were Ordinal Level 3; 41.8% were Ordinal Level 4. • Median time from symptom onset to randomization was 7 days. • 23.3% to 23.9% of patients received oseltamivir. **Outcomes:** • No significant difference in the odds of worse clinical status at Day 15 between 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.	with mild or moderate COVID-19.

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Study Design	Methods	Results	Limitations and Interpretation
Hydroxychloroquine in Nonhospitalized Adults With Early COVID-19[24]			
Randomized, placebo-controlled trial in nonhospitalized adults (n = 491)	**Key Inclusion Criteria:** • Symptoms that were compatible with COVID-19 and lasted ≤4 days • 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 6–8 hours, then HCQ 600 mg once daily for 4 days • Placebo **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, measured by a 10-point, self-reported, visual analogue scale	**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. **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 between the arms (4 patients in the HCQ arm vs. 10 patients in placebo arm); 2 of 10 placebo participants were hospitalized for reasons that were unrelated to COVID-19 • A higher percentage of patients in HCQ arm experienced AEs than patients in placebo arm (43% vs. 22%; $P < 0.001$).	**Key Limitations:** • This study enrolled a highly heterogeneous 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 analogue scales are not commonly used, and their ability to assess acute viral respiratory infections in clinical trials has not been validated. **Interpretation:** • The study has some limitations, and it did not find evidence that early administration of HCQ reduced symptom severity in patients with mild COVID-19.

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Study Design	Methods	Results	Limitations and Interpretation
Hydroxychloroquine in Nonhospitalized Adults With Mild COVID-19[25]			
Open-label RCT in nonhospitalized adults (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 (control arm) **Primary Endpoint:** • Reduction in SARS-CoV-2 viral load, assessed using NP swabs on Days 3 and 7 **Secondary Endpoints:** • Disease progression up to Day 28 • Time to complete resolution of symptoms	**Number of Participants:** • ITT analysis: HCQ (n = 136) and control (n = 157) • 60 patients were excluded from the ITT analysis due to negative baseline RT-PCR, missing RT-PCR at follow-up visits, or consent withdrawal. **Participant Characteristics:** • Mean age was 41.6 years. • 67% of patients were woman. • Majority of patients were health care workers (87%). • 53% of patients reported chronic health conditions. • Median time from symptom onset to enrollment was 3 days (IQR 2–4 days). • Most common COVID-19 symptoms were fever, cough, and sudden olfactory loss. **Outcomes:** • No significant difference in viral load reduction between control arm and HCQ arm at Day 3 • (-1.41 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.	**Key Limitations:** • Open-label, non-placebo-controlled trial • Study design allowed for the possibility of dropouts in control arm and over-reporting of AEs in HCQ arm. • The intervention changed during the study; the authors initially planned to include HCQ plus DRV/COBI. • The majority of the participants were relatively young health care workers. **Interpretation:** • Early administration of HCQ to patients with mild COVID-19 did not result in improvement in virologic clearance, a lower risk of disease progression, or a reduced time to symptom improvement.

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Study Design	Methods	Results	Limitations and Interpretation
Observational Study on Hydroxychloroquine With or Without Azithromycin[26]			
Retrospective, multicenter, observational study in a random sample of hospitalized adults 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 **Secondary Endpoint:** • Cardiac arrest and arrhythmia or QT prolongation on an ECG	**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. • 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).	**Key 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 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[27]			
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 ED) 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)	**Key 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.

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Key: AE = adverse event; AV = atrioventricular; AZM = azithromycin; CPR = cardiopulmonary resuscitation; CQ = chloroquine; DRV/COBI = darunavir/cobicistat; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; ED = emergency department, FiO_2 = fraction of inspired oxygen; GI = gastrointestinal; HCQ = hydroxychloroquine; HFNC = high-flow nasal cannula; ICU = intensive care unit; IFN = interferon; IMV = invasive mechanical ventilation; ITT = intention-to-treat; LPV/RTV = lopinavir/ritonavir; mITT = modified intention-to-treat; NP = nasopharyngeal; the Panel = the COVID-19 Treatment Guidelines Panel; PCR = polymerase chain reaction; PO = orally; RCT = randomized controlled trial; RDV = remdesivir; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SOC = standard of care

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Interferons

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Interferons are a family of cytokines with in vitro and in vivo antiviral properties. Interferon beta-1a has been approved by the Food and Drug Administration (FDA) to treat relapsing forms of multiple sclerosis, and it has been evaluated in clinical trials for the treatment of COVID-19. Interferon alfa has been approved to treat hepatitis B and hepatitis C virus infections, and interferon lambda is not currently approved by the FDA for any use. Both interferon alfa and lambda have also been evaluated for the treatment of COVID-19.

Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of **systemic interferon beta** for the treatment of hospitalized patients with COVID-19 **(AI)**.
- The Panel **recommends against** the use of **interferon alfa** or **lambda** for the treatment of hospitalized patients with COVID-19, except in a clinical trial **(AIIa)**.
- The Panel **recommends against** the use of **interferons** for the treatment of nonhospitalized patients with mild or moderate COVID-19, except in a clinical trial **(AIIa)**.

Rationale

Many of the early studies that evaluated the use of systemic interferons for the treatment of COVID-19 were conducted in early 2020, before the widespread use of remdesivir and corticosteroids. In addition, these early studies administered interferons with other drugs that have since been shown to have no clinical benefit in people with COVID-19, such as lopinavir/ritonavir and hydroxychloroquine.[1-3]

More recent studies have not demonstrated efficacy for interferons in the treatment of COVID-19, and some of the trials suggested potential harm in patients with severe disease, such as those who were on high-flow oxygen, noninvasive ventilation, or mechanical ventilation.[4,5] In a large randomized controlled trial of hospitalized patients with COVID-19, the combination of interferon beta-1a plus remdesivir showed no clinical benefit when compared to remdesivir alone.[4] Similarly, the World Health Organization Solidarity trial did not show a benefit for interferon beta-1a when this drug was administered to hospitalized patients, approximately 50% of whom were on corticosteroids.[5]

Other interferons, including systemic interferon alfa or lambda and inhaled interferons, have also been evaluated in patients with COVID-19; however, these interferons (with the exception of subcutaneous interferon alfa) are not available in the United States. The trials that have evaluated interferon alfa and interferon lambda have generally been small or moderate in size and have not been adequately powered to assess whether these agents provide a clinical benefit for patients with COVID-19 (see Table 2c).

Clinical Trials

See ClinicalTrials.gov for a list of clinical trials that are evaluating the use of interferons for the treatment of COVID-19.

Adverse Effects

The most frequent adverse effects of systemic interferon include flu-like symptoms, nausea, fatigue, weight loss, hematological toxicities, elevated transaminases, and psychiatric problems (e.g., depression, suicidal ideation). Interferon beta is better tolerated than interferon alfa, but it can cause similar types of adverse effects.[6,7]

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Drug-Drug Interactions

Additive toxicities may occur when systemic interferons are used concomitantly with other immunomodulators and chemotherapeutic agents.[6,7]

Considerations in Pregnancy

According to analyses of data from several large pregnancy registries, exposure to interferon beta-1b prior to conception or during pregnancy does not lead to an increased risk of adverse birth outcomes (e.g., spontaneous abortion, congenital anomaly).[8,9] Exposure to interferon beta-1b did not influence birth weight, height, or head circumference.[10]

Considerations in Children

There are currently not enough data on the use of interferons to treat respiratory viral infections in children to make any recommendations for treating children with COVID-19.

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Table 2c. Interferons: Selected Clinical Data

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

Methods	Results	Limitations and Interpretation
ACTT-3: Multinational, Double-Blind RCT of Interferon Beta-1a and Remdesivir in Hospitalized Adults With COVID-19[1]		

Key Inclusion Criteria:
• Evidence of pneumonia (radiographic infiltrates, SpO_2 ≤94% on room air, or supplemental oxygen)
• No MV required
Key Exclusion Criteria:
• AST or ALT >5 times ULN
• Impaired renal function
• Anticipated hospital discharge or transfer within 72 hours
Interventions:
• RDV 200 mg IV on Day 1, then RDV 100 mg IV once daily for 9 days plus IFN beta-1a 44 µg SQ every other day for up to 4 doses (n = 487)
• RDV 200 mg IV on Day 1, then RDV 100 mg IV once daily for 9 days plus placebo (n = 482)
Primary Endpoint:
• Time to recovery by Day 28
Key Secondary Endpoints:
• Clinical status at Day 14, as measured by an OS
• Mortality by Day 28
	Participant Characteristics:
	• Mean age 59 years; 38% were aged ≥65 years
	• 58% men; 32% Latino, 60% White, 17% Black
	• Mean of 8.6 days of symptoms before enrollment
	• 90% had ≥1 comorbidity; 58% with HTN; 58% with obesity; 37% with DM
	Primary Outcome:
	• Median time to recovery for both arms was 5 days (rate ratio 0.99; 95% CI, 0.87–1.13; *P* = 0.88).
	  • In patients on high-flow oxygen or NIV (OS6) at baseline, median time to recovery was >28 days in IFN beta-1a arm and 9 days in placebo arm (rate ratio 0.40; 95% CI, 0.22–0.75; *P* = 0.0031).
	Secondary Outcomes:
	• No difference between arms in clinical improvement at 14 days (OR 1.01; 95% CI, 0.79–1.28).
	• No difference between arms in mortality by Day 28 in:
	  • All patients: 5% vs. 3% (HR 1.33; 95% CI, 0.69–2.55)
	  • Patients with OS6 at baseline: 21% vs. 12% (HR 1.74; 95% CI, 0.51–5.93)
		Key Limitation:
		• OS6 patients were excluded after 270 patients were enrolled because of an increased frequency of AEs in this group
		Interpretation:
		• There was no clinical benefit of IFN beta-1a plus RDV in hospitalized patients compared to RDV alone.
		• The use of IFN beta-1a was associated with worse outcomes among patients who were OS6 at baseline.

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Methods	Results	Limitations and Interpretation
WHO Solidarity Trial: Multinational, Open-Label, Adaptive RCT of IV or SQ Interferon Beta-1a or Other Repurposed Drugs in Hospitalized Adults With COVID-19[2]		
Key Inclusion Criteria: • Diagnosis of COVID-19 • Not expected to be transferred elsewhere within 72 hours **Interventions:** • IFN beta-1a 44 µg SQ on day of randomization, Day 3, and Day 6 (n = 1,656) • IFN beta-1a 10 µg IV daily for 6 days for patients on high-flow oxygen, ventilation, or ECMO (n = 394) • IFN beta-1a (either SQ or IV) and LPV/RTV 400 mg/50 mg twice daily for 14 days (n = 651) • Local SOC (n = 2,050) **Primary Endpoint:** • In-hospital mortality **Key Secondary Endpoint:** • Initiation of ventilation	**Participant Characteristics:** • 35% aged <50 years; 19% aged ≥70 years; 63% men • 70% on supplemental oxygen; 7% on ventilation • Approximately 50% received corticosteroids during the study **Primary Outcomes:** • In-hospital mortality was 11.9% for combined IFN beta-1a arms and 10.5% in SOC arm (rate ratio 1.16; 95% CI, 0.96–1.39). • For IFN beta-1a only (without LPV/RTV) recipients vs. SOC recipients, rate ratio was 1.12 (95% CI, 0.83–1.51). • Among those on ventilation at entry, age-stratified rate ratio for in-hospital mortality was 1.40 (95% CI, 0.93–2.11). **Secondary Outcome:** • 10% initiated ventilation in the combined IFN beta-1a arms and SOC arm.	**Key Limitations:** • Open-label study • IFN beta-1a given as IV or SQ formulations at different doses **Interpretation:** • IFN beta-1a does not improve mortality for hospitalized patients.

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Methods	Results	Limitations and Interpretation
DisCoVeRy Solidarity Trial Add-On: Open-Label, Adaptive RCT of SQ Interferon Beta-1a Plus Lopinavir/Ritonavir, Lopinavir/Ritonavir, or Hydroxychloroquine in Hospitalized Adults With COVID-19 in France[3]		

Key Inclusion Criteria:
• Positive PCR result for SARS-CoV-2
• Patients had pulmonary rales or crackles with SpO_2 ≤94% or they required supplemental oxygen
Interventions:
• IFN beta-1a 44 ug SQ on Days 1, 3, and 6 plus LPV/RTV 400 mg/100 mg PO twice daily for 14 days plus SOC (n = 145)
• LPV/RTV 400 mg/100 mg PO twice daily for 14 days plus SOC (n = 145)
• HCQ 400 mg twice on Day 1, then HCQ 400 mg daily for 9 days plus SOC (n = 145)
• SOC alone, which included corticosteroids, anticoagulants, or immunomodulatory agents but not antivirals (n = 148)
Primary Endpoint:
• Clinical status at Day 15, as measured by an OS
Key Secondary Endpoints:
• Clinical status at Day 29
• Rate of SARS-CoV-2 viral clearance
• Time to SARS-CoV-2 viral clearance
• Time to improvement of 2 OS categories
• Time to hospital discharge
	Participant Characteristics:
	• Median age 63 years; 72% men
	• 29% were obese; 26% with chronic cardiac disease; 22% with DM
	• 36% had severe disease
	• Median of 9 days from symptom onset to randomization
	• 30% received steroids during the study
	Primary Outcome:
	• No difference in clinical status at Day 15 for any intervention compared to SOC:
	  • IFN beta-1a plus LPV/RTV: aOR 0.69 (95% CI, 0.45–1.04; *P* = 0.08)
	  • LPV/RTV: aOR 0.83 (95% CI, 0.55–1.26; *P* = 0.39)
	  • HCQ: aOR 0.93 (95% CI, 0.62–1.41; *P* = 0.75)
	Secondary Outcomes:
	• No difference in clinical status at Day 29 between the arms.
	• No difference in rate and time to SARS-CoV-2 viral clearance between the arms.
	• Time to 2 OS-category improvement and hospital discharge by Day 29 was longer in LPV/RTV plus IFN beta-1a and LPV/RTV arms than in SOC arm.
		Key Limitations:
		• Open-label study
		• Most patients had moderate disease
		• No IFN beta-1a arm without LPV/RTV
		• Study stopped early for futility
		Interpretation:
		• Compared to SOC alone, the use of IFN-beta-1a plus LPV/RTV did not improve clinical status, rate of viral clearance, or time to viral clearance in hospitalized patients with COVID-19.

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Methods	Results	Limitations and Interpretation
Single-Blind RCT of Peginterferon Lambda-1a for Treatment of Outpatients With Uncomplicated COVID-19 in the United States[4]		

Key Inclusion Criteria:
• Aged 18–65 years
• Asymptomatic or symptomatic
• Positive RT-PCR result for SARS-CoV-2 within 72 hours of enrollment
Key Exclusion Criteria:
• Current or imminent hospitalization
• Respiratory rate >20 breaths/min
• SpO_2 <94% on room air
• Decompensated liver disease
Interventions:
• Single dose of PEG-IFN lambda-1a 180 µg SQ (n = 60)
• Placebo (n = 60)
Primary Endpoint:
• Time to first negative SARS-CoV-2 RT-PCR result
Key Secondary Endpoints:
• Hospitalizations by Day 28
• Time to complete symptom resolution
	Participant Characteristics:
	• Median age 36 years; 42% women; 63% Latinx, 28% White
	• 7% were asymptomatic
	• Median of 5 days of symptoms before randomization
	Primary Outcome:
	• Median time to cessation of viral shedding was 7 days in both arms (aHR 0.81; 95% CI, 0.56–1.19; *P* = 0.29).
	Secondary Outcomes:
	• No difference between PEG-IFN lambda-1a and placebo arms in:
	  • Proportion of patients hospitalized by Day 28: 3.3% for each arm
	  • Time to resolution of symptoms: 8 days vs. 9 days (HR 0.94; 95% CI, 0.64–1.39)
	Other Outcomes:
	• Patients who received PEG-IFN lambda-1a were more likely to have transaminase elevations than patients who received placebo (25% vs. 8%; *P* = 0.027).
		Key Limitation:
		• Small sample size
		Interpretation:
		• PEG-IFN lambda-1a provided no virologic or clinical benefit compared to placebo among outpatients with uncomplicated COVID-19.

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Methods	Results	Limitations and Interpretation
Double-Blind RCT of Peginterferon Lambda in Outpatients With Laboratory-Confirmed COVID-19 in Canada[5]		
Key Inclusion Criteria: • Positive SARS-CoV-2 PCR result • Patients were within 7 days of symptom onset, or, if asymptomatic, were within 7 days of first positive SARS-CoV-2 test result **Key Exclusion Criterion:** • Immunosuppression or condition that could be worsened by PEG-IFN lambda **Interventions:** • Single dose of PEG-IFN lambda 180 µg SQ (n = 30) • Placebo (n = 30) **Primary Endpoint:** • Proportion of participants with negative nasal mid-turbinate swab for SARS-CoV-2 at Day 7 **Key Secondary Endpoints:** • Quantitative change in SARS-CoV-2 RNA over time • Hospitalizations by Day 14	**Participant Characteristics:** • Median age 46 years; 58% women; 52% White • 19% were asymptomatic • Mean of 4.5 days of symptoms before randomization **Primary Outcome:** • 80% in PEG-IFN lambda arm and 63% in placebo arms were negative for SARS-CoV-2 RNA at Day 7 ($P = 0.15$). **Secondary Outcomes:** • VL decline by Day 7 was greater in PEG-IFN lambda arm than in placebo arm ($P = 0.0041$). • 1 participant in each arm was admitted to the hospital by Day 14. **Other Outcomes:** • 3 participants in each arm had mild elevation of aminotransferase concentrations. Increase was greater in PEG-IFN lambda arm.	**Key Limitation:** • Small sample size **Interpretation:** • PEG-IFN lambda may accelerate VL decline and clearance in outpatients with COVID-19; however, the clinical significance of this finding is unclear.

Key: AE = adverse event; ALT = alanine transaminase; AST = aspartate aminotransferase; DM = diabetes mellitus; ECMO = extracorporeal membrane oxygenation; HCQ = hydroxychloroquine; HTN = hypertension; IFN = interferon; IV = intravenous; LPV/RTV = lopinavir/ritonavir; MV = mechanical ventilation; NIV = noninvasive ventilation; OS = ordinal scale; the Panel = the COVID-19 Treatment Guidelines Panel; PCR = polymerase chain reaction; PEG-IFN = pegylated interferon; RCT = randomized controlled trial; RDV = remdesivir; RT-PCR = reverse transcription polymerase chain reaction; SOC = standard of care; SpO_2 = oxygen saturation; SQ = subcutaneous; ULN = upper limit of normal; VL = viral load

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Ivermectin

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Ivermectin is a Food and Drug Administration (FDA)-approved antiparasitic drug used to treat several neglected tropical diseases, including onchocerciasis, helminthiases, and scabies.[1] For these indications, ivermectin has been widely used and is generally well-tolerated.[1,2] 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 host importin alpha/beta-1 nuclear transport proteins, which are part of a key intracellular transport process.[3,4] Viruses hijack the process and enhance infection by suppressing the host's antiviral response. In addition, ivermectin docking may interfere with SARS-CoV-2 spike protein attachment to the human cell membrane.[5] Some studies of ivermectin have also reported potential anti-inflammatory properties, which have been postulated to be beneficial in people with COVID-19.[6-8]

Ivermectin has been shown to inhibit replication of SARS-CoV-2 in cell cultures.[9] 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.[10,11] Although ivermectin appears to accumulate in lung tissue, predicted systemic plasma and lung tissue concentrations are much lower than 2 µM, the half-maximal inhibitory concentration (IC_{50}) observed in vitro for ivermectin against SARS-CoV-2.[12-15] Subcutaneous administration of ivermectin 400 µg/kg had no effect on SARS-CoV-2 viral loads in hamsters.[16] 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.

The safety and efficacy of ivermectin for the prevention and treatment of COVID-19 have been evaluated in clinical trials and observational cohorts. Summaries of the studies that informed The COVID-19 Treatment Guidelines Panel's (the Panel) recommendation can be found in Table 2d. The Panel reviewed additional studies, but these studies are not summarized in Table 2d because they have study design limitations or results that make them less definitive and informative.

Recommendation

- The Panel **recommends against** the use of **ivermectin** for the treatment of COVID-19, except in clinical trials **(AIIa)**.

Rationale

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. Most of these studies, especially studies completed earlier in the pandemic, had incomplete information and significant methodological limitations, which made excluding common causes of bias difficult. Many of these studies have not been peer reviewed, and some have now been retracted.

The Panel's recommendation is primarily informed by recently published randomized controlled trials.[17-20] The primary outcomes of these trials showed that the use of ivermectin for the treatment of COVID-19 had no clinical benefit. In TOGETHER, an adaptive platform trial conducted in Brazil, there was no apparent difference between the ivermectin and placebo arms for the primary outcome of risk

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of emergency department visits or hospitalization (14.7% vs. 16.4%). Also, there was no statistically significant difference between the ivermectin and placebo arms in mortality (3.1% vs. 3.5%).

I-TECH, an open-label trial conducted in Malaysia, found no difference between the ivermectin and standard of care arms (21.6% vs. 17.3%) for the primary outcome of risk of progression to severe disease. The ivermectin arm had a lower risk of mortality than the standard of care arm (1.2% vs. 4.0%), but this difference was not statistically significant.

The study populations of both the TOGETHER and I-TECH trials were patients with mild to moderate disease, and the number of deaths was low (as expected). In these randomized trials, completely excluding an effect of ivermectin is difficult, because the trials were not powered to detect differences in secondary outcomes, such as death. However, data from these trials do not provide evidence that the use of ivermectin benefited the treatment of COVID-19.

Comparisons of the efficacy of ivermectin for the treatment of COVID-19 are complicated by the large variability of doses and durations of treatment used in the studies. There have been concerns that doses in early trials were too low and durations of treatment were too short. However, the higher doses (300 µg/kg–400 µg/kg per day for up to 3–5 days) used in the more recent TOGETHER and I-TECH trials did not demonstrate clinical benefit.

Although there have been many ivermectin studies, only a few trials have been adequately powered, well-designed, and well-conducted. More recent clinical trials address the limitations of earlier studies but fail to show clear evidence that ivermectin reduces time to recovery or prevents COVID-19 disease progression. For this reason, and because several medications now have demonstrated clinical benefit for the treatment of COVID-19, the Panel **recommends against** the use of **ivermectin** for the treatment of COVID-19, except in a clinical trial **(AIIa)**. Additional adequately powered, well-designed, and well-conducted trials are needed to evaluate the effect of ivermectin on COVID-19. The Panel will continue to review emerging data on ivermectin use, including the results from 2 large, ongoing randomized controlled trials.

See Table 2d for summaries of the key studies that informed the Panel's recommendation.

Monitoring, Adverse Effects, and Drug-Drug Interactions

- Adverse effects of ivermectin may include dizziness, pruritis, nausea, or diarrhea.[21]
- 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.[22]
- Ivermectin is a minor cytochrome P450 3A4 substrate and a p-glycoprotein substrate.
- Ivermectin is generally given with water on an empty stomach; however, administering ivermectin with food increases its bioavailability.
- The FDA first issued a warning in April 2020 that ivermectin intended for use in animals **should not be used** to treat COVID-19 in humans. This warning was updated and reiterated in 2021.

Clinical Trials

Several clinical trials 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 2d. Ivermectin: Selected Clinical Data

Last Updated: April 29, 2022

The clinical trials described in this table are RCTs that had the greatest impact on the Panel's recommendation. The Panel reviewed other clinical studies of IVM for the treatment of COVID-19.[1-26] However, those studies have limitations that make them less definitive and informative than the studies summarized in the table.

Methods	Results	Limitations and Interpretation
TOGETHER: Double-Blind, Adaptive, RCT of Ivermectin in Nonhospitalized Patients With COVID-19 in Brazil[27]		

Key Inclusion Criteria:
• Positive SARS-CoV-2 antigen test
• Within 7 days of symptom onset
• ≥1 high-risk factor for disease progression (e.g., aged >50 years, comorbidities, immunosuppression)
Interventions:
• IVM 400 µg/kg PO per day for 3 days (n = 679)
• Placebo (n = 679; not all participants received IVM placebo)
Primary Endpoint:
• Composite of emergency setting observation >6 hours or hospitalized for COVID-19 within 28 days of randomization
Key Secondary Endpoints:
• Viral clearance at Day 7
• All-cause mortality
• Occurrence of AEs
	Participant Characteristics:
	• Median age 49 years; 46% aged ≥50 years; 58% women; 95% "mixed race"
	• Most prevalent risk factor: 50% with obesity
	• Symptom onset: 44% within 3 days
	Primary Outcome:
	• Composite of emergency setting observation >6 hours or hospitalized within 28 days of randomization (ITT): 100 (14.7%) in IVM arm vs. 111 (16.4%) in placebo arm (relative risk 0.90; 95% CrI, 0.70–1.16)
	  • 171 (81%) of all events were hospitalizations (ITT)
	Secondary Outcomes:
	• No difference between IVM and placebo arms in:
	  • Viral clearance at Day 7 (relative risk 1.00; 95% CrI, 0.68–1.46)
	  • All-cause mortality: 21 (3.1%) vs. 24 (3.5%) (relative risk 0.88; CrI, 0.49–1.55)
	  • Occurrence of AEs
		Key Limitations:
		• Health care facility capacity may have influenced the number and duration of emergency setting visits and hospitalizations.
		• No details on safety outcomes (e.g., type of treatment-emergent AEs) other than grading were reported.
		Interpretation:
		• In outpatients with recent COVID-19 infection, IVM did not reduce the need for emergency setting visits or hospitalization when compared with placebo.

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Methods	Results	Limitations and Interpretation
IVERCOR-COVID19: Double-Blind, Placebo-Controlled, Randomized Trial of Ivermectin in Nonhospitalized Patients With COVID-19 in Argentina[28]		
Key Inclusion Criterion: • Positive SARS-CoV-2 RT-PCR result within 48 hours of screening **Key Exclusion Criteria:** • Oxygen supplementation or hospitalization • Concomitant use of CQ or HCQ **Interventions:** • Weight-based dose of IVM PO at enrollment and 24 hours later for a maximum total dose of 48 mg (n = 250) • Placebo (n = 251) **Primary Endpoint:** • Hospitalization for any reason **Key Secondary Endpoints:** • Need for MV • All-cause mortality • Occurrence of AEs	**Participant Characteristics:** • Mean age 42 years; 8% aged ≥65 years; 47% women • 24% with HTN; 10% with DM; 58% with ≥1 comorbidity • Median time from symptom onset: 4 days **Primary Outcome:** • Hospitalization for any reason: 5.6% in IVM arm vs. 8.3% in placebo arm (OR 0.65; 95% CI, 0.32–1.31; P = 0.23) **Secondary Outcomes:** • Need for MV: 2% in IVM arm vs. 1% in placebo arm (P = 0.7) • All-cause mortality: 2% in IVM arm vs. 1% in placebo arm (P = 0.7) • Occurrence of AEs: 18% in IVM arm vs. 21% in placebo arm (P = 0.6)	**Key Limitation:** • Enrolled a fairly young population with few of the comorbidities that predict disease progression. **Interpretation:** • Among patients who had recently acquired SARS-CoV-2 infection, there was no evidence that IVM provided any clinical benefit.

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Methods	Results	Limitations and Interpretation
I-TECH: Open-Label RCT of Ivermectin in Patients With Mild to Moderate COVID-19 in Malaysia[29]		

Key Inclusion Criteria:
• Positive SARS-CoV-2 RT-PCR or antigen test result within 7 days of symptom onset
• Aged ≥50 years
• ≥1 comorbidity
Key Exclusion Criteria:
• Required supplemental oxygen
• Severe hepatic impairment (ALT >10 times the ULN)
Interventions:
• IVM: 400 µg/kg PO daily for 5 days plus SOC (n = 241)
• SOC (n = 249)
Primary Endpoint:
• Progression to severe COVID-19 (i.e., hypoxia requiring supplemental oxygen to maintain SpO_2 ≥95%)
Key Secondary Endpoints:
• In-hospital, all-cause mortality by Day 28
• MV or ICU admission
• Occurrence of AEs
	Participant Characteristics:
	• Mean age 63 years; 55% women
	• 68% received ≥1 dose COVID-19 vaccine; 52% received 2 doses
	• Most common comorbidities: 75% with HTN; 54% with DM; 24% with dyslipidemia
	• Mean duration of symptoms: 5 days
	Primary Outcome:
	• Progression to severe COVID-19 (mITT): 52 (21.6%) in IVM plus SOC arm vs. 43 (17.3%) in SOC alone arm (relative risk 1.25; 95% CI, 0.87–1.80; *P* = 0.25)
	Secondary Outcomes:
	• No difference between IVM plus SOC arm and SOC alone arm in:
	  • In-hospital, all-cause mortality: 3 (1.2%) vs. 10 (4.0%) (relative risk 0.31; 95% CI, 0.09–1.11; *P* = 0.09)
	  • MV: 4 (1.7%) vs. 10 (4.0%) (relative risk 0.41; 95% CI, 0.13–1.30; *P* = 0.17)
	  • ICU admission: 6 (2.5%) vs. 8 (3.2%) (relative risk 0.78; 95% CI, 0.27–2.20; *P* = 0.79)
	• Occurrence of AEs: 33 (13.7%) in the IVM plus SOC arm vs. 11 (4.4%) in the SOC alone arm; most with diarrhea (14 vs. 4)
		Key Limitation:
		• Open-label study
		Interpretation:
		• In patients with mild to moderate COVID-19, there was no evidence that IVM provided any clinical benefit, including no evidence that IVM reduced progression to severe disease.

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Methods	Results	Limitations and Interpretation
Double-Blind, Placebo-Controlled, Randomized Trial of Ivermectin in Patients With Mild COVID-19 in Colombia[30]		

Key Inclusion Criteria:
• Positive SARS-CoV-2 RT-PCR or antigen test result
• Symptoms ≤7 days
• Mild disease
Key Exclusion Criteria:
• Asymptomatic disease
• Severe pneumonia
• Hepatic dysfunction
Interventions:
• IVM 300 µg/kg PO per day for 5 days (n = 200)
• Placebo PO (n = 198)
Primary Endpoint:
• Time to resolution of symptoms within 21 days
Key Secondary Endpoints:
• Clinical deterioration
• Escalation of care
• Occurrence of AEs
	Participant Characteristics:
	• Median age 37 years; 4% aged ≥65 years in IVM arm, 8% in placebo arm; 39% men in IVM arm, 45% in placebo arm
	• 79% with no known comorbidities
	• Median symptom onset to randomization: 5 days
	Primary Outcome:
	• Median time to symptom resolution: 10 days in IVM arm vs. 12 days in placebo arm (HR 1.07; $P = 0.53$)
	  • Symptoms resolved by Day 21: 82% in IVM arm vs. 79% in placebo arm
	Secondary Outcomes:
	• Clinical deterioration: no difference between arms
	• Escalation of care: no difference between arms
	• Occurrence of AEs:
	  • Discontinued treatment due to AEs: 8% in IVM arm vs. 3% in placebo arm
	  • No SAEs were related to intervention
		Key Limitations:
		• Due to low event rates, the primary endpoint changed from the proportion of patients with clinical deterioration to the time to symptom resolution during the trial.
		• The study enrolled younger, healthier patients, a population that does not typically develop severe COVID-19.
		Interpretation:
		• In patients with mild COVID-19, IVM 300 µg/kg per day for 5 days did not improve the time to resolution of symptoms.

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Methods	Results	Limitations and Interpretation
Open-Label RCT of Ivermectin in Hospitalized Patients With COVID-19 in Egypt[31]		
Key Inclusion Criteria: • RT-PCR-confirmed SARS-CoV-2 infection by pharyngeal swab • Hospitalized with mild to moderate COVID-19 **Key Exclusion Criterion:** • Cardiac problems **Interventions:** • IVM 12 mg PO once daily for 3 days (n = 82) • SOC (n = 82) **Primary Endpoint:** • All-cause mortality by 28 days **Key Secondary Endpoints:** • Hospital LOS • Need for MV	**Participant Characteristics:** • Mean age 42 years for IVM arm, 39 years for SOC arm; 50% men • 49% with ≥1 comorbidity **Primary Outcome:** • All-cause mortality by 28 days: 3 (3.7%) in IVM arm vs. 4 (4.9%) in SOC arm ($P = 1.00$) **Secondary Outcomes:** • Mean hospital LOS: 9 days in IVM arm vs. 11 days in SOC arm ($P = 0.085$) • Need for MV: 3 (3.7%) in each arm ($P = 1.00$)	**Key Limitation:** • Small, open-label study **Interpretation:** • Use of IVM, when compared with the SOC, did not result in differences in all-cause mortality, hospital LOS, or the need for MV.

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Methods	Results	Limitations and Interpretation
Double-Blind, Placebo-Controlled, Randomized Trial of Ivermectin in Patients With Mild to Moderate COVID-19 in India[32]		
Key Inclusion Criteria: • Positive SARS-CoV-2 RT-PCR or antigen test result • Hospitalized with mild or moderate COVID-19 **Interventions:** • IVM 12 mg PO for 2 days (n = 55) • Placebo PO (n = 57) **Primary Endpoint:** • Negative SARS-CoV-2 RT-PCR result on Day 6 **Key Secondary Endpoints:** • Symptom resolution by Day 6 • Discharge by Day 10 • Need for ICU admission or MV • In-hospital mortality	**Participant Characteristics:** • Mean age 53 years; 28% women • 35% with HTN; 36% with DM • 79% with mild COVID-19 • Mean 6.9 days from symptom onset • 100% received HCQ, steroids, and antibiotics; 21% received RDV; 6% received tocilizumab **Primary Outcome:** • Negative RT-PCR result on Day 6: 24% in IVM arm vs. 32% in placebo arm (rate ratio 0.8; $P = 0.348$) **Secondary Outcomes:** • Symptom resolution by Day 6: 84% in IVM arm vs. 90% in placebo arm (rate ratio 0.9; $P = 0.36$) • Discharge by Day 10: 80% in IVM arm vs. 74% in placebo arm (rate ratio 1.1; $P = 0.43$) • Need for ICU admission or MV: no difference between arms • In-hospital mortality: 0 in IVM arm (0%) vs. 4 in placebo arm (7%)	**Key Limitations:** • Although the primary endpoint was a negative SARS-CoV-2 RT-PCR result on Day 6, no RT-PCR result or an inconclusive RT-PCR result was reported for 42% of patients in the IVM arm and 23% in the placebo arm. • The time to discharge was not reported, and outcomes after discharge were not evaluated. **Interpretation:** • IVM provided no significant virologic or clinical benefit for patients with mild to moderate COVID-19.

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Methods	Results	Limitations and Interpretation
RIVET-COV: Double-Blind, Placebo-Controlled, Randomized Trial of Ivermectin in Patients With Mild to Moderate COVID-19 in India[33]		
Key Inclusion Criteria: • Positive SARS-CoV-2 RT-PCR or antigen test result • Nonsevere COVID-19 **Key Exclusion Criteria:** • CrCl <30 mL/min • Transaminases >5 times ULN • MI, heart failure, QTc interval prolongation • Severe comorbidity **Interventions:** • Single dose of IVM 24 mg PO (n = 51) • Single dose of IVM 12 mg PO (n = 49) • Placebo (n = 52) **Primary Endpoints:** • Negative RT-PCR result at Day 5 • Decline of VL at Day 5 **Key Secondary Endpoints:** • Time to symptom resolution • Clinical worsening at Day 14 • Number of hospital-free days at Day 28 • Frequency of AEs	**Participant Characteristics:** • Mean age 35 years; 89% men • 60% to 68% with mild COVID-19 (including asymptomatic patients); 33% to 40% with moderate COVID-19 • Median duration of symptoms: 4–5 days, similar across arms • 10% received concurrent antivirals (RDV, favipiravir, or HCQ); no difference across arms **Primary Outcomes:** • Negative RT-PCR result at Day 5: 48% in IVM 24 mg arm vs. 35% in IVM 12 mg arm vs. 31% in placebo arm (P = 0.30) • Decline of VL at Day 5: no significant difference between arms **Secondary Outcomes:** • Time to symptom resolution: no difference between arms • Clinical worsening at Day 14: 8% in IVM 24 mg arm vs. 5% in IVM 12 mg arm vs. 11% in placebo arm (P = 0.65) • Number of hospital-free days at Day 28: no difference between arms • Frequency of AEs: no difference between arms; no SAEs	**Key Limitation:** • Small sample size **Interpretation:** • For patients who received IVM and those who received placebo, there was no difference in the proportion of negative RT-PCR results at Day 5 or clinical outcomes.

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Methods	Results	Limitations and Interpretation
COVER: Phase 2, Double-Blind RCT of Ivermectin in Nonhospitalized Patients With COVID-19 in Italy[34]		
Key Inclusion Criteria: • Asymptomatic or oligosymptomatic disease • SARS-CoV-2 infection confirmed by RT-PCR result • Not hospitalized or receiving supplemental oxygen **Key Exclusion Criteria:** • CNS disease • Receiving dialysis • Severe medical condition with <6 months survival prognosis • Use of warfarin, antiviral agents, CQ, or HCQ **Interventions:** • IVM 1,200 µg/kg PO once daily for 5 days (n = 32) • IVM 600 µg/kg plus placebo PO once daily for 5 days (n = 29) • Placebo PO (n = 32) **Primary Endpoints:** • Number of SAEs • Change in VL at Day 7	**Participant Characteristics:** • Median age 47 years; 58% men • 86% with symptoms **Primary Outcomes:** • Number of SAEs: 0 • Mean $\log_{10}$ reduction in VL at Day 7: 2.9 in IVM 1,200 µg/kg arm vs. 2.5 in IVM 600 µg/kg arm vs. 2.0 in placebo arm (IVM 1,200 µg/kg vs. placebo, $P = 0.099$; IVM 600 µg/kg vs. placebo, $P = 0.122$) **AE Outcomes:** • 14 (15.1%) discontinued treatment: 11 (34.4%) in IVM 1,200 µg/kg arm vs. 2 (6.9%) in IVM 600 µg/kg arm vs. 1 (3.1%) in placebo arm • All discontinuations in IVM 1,200 µg/kg arm due to tolerability	**Key Limitations:** • Small, Phase 2 study • 90% of subjects screened were not enrolled for various reasons. • Recruitment stopped early because of decline in the number of COVID-19 cases. **Interpretations:** • A high dose of IVM (1,200 µg/kg) appears to be safe but not well-tolerated; 34% discontinued therapy due to AEs. • There was no significant difference in reduction of VL between IVM and placebo arms.

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Methods	Results	Limitations and Interpretation
Double-Blind RCT of Ivermectin, Chloroquine, or Hydroxychloroquine in Hospitalized Adults With Severe COVID-19 in Brazil[35]		

Key Inclusion Criteria:
• Hospitalized with laboratory-confirmed SARS-CoV-2 infection
• ≥1 of the following severity criteria:
  • Dyspnea
  • Tachypnea (>30 breaths/min)
  • SpO_2 <93%
  • PaO_2/FiO_2 <300 mm Hg
  • Involvement of >50% of lungs by CXR or CT
Key Exclusion Criterion:
• Cardiac arrhythmia
Interventions:
• IVM 14 mg once daily for 3 days (n = 53)
• CQ 450 mg twice daily on Day 0, then once daily for 4 days (n = 61)
• HCQ 400 mg twice daily on Day 0, then once daily for 4 days (n = 54)
Endpoints:
• Need for supplemental oxygen, MV, or ICU admission
• Occurrence of AEs
• Mortality
	Participant Characteristics:
	• Mean age 53 years; 58% men
	• Most common comorbidities: 43% with HTN; 28% with DM; 38% with BMI >30
	• 76% with respiratory failure on admission
	Outcomes:
	• No difference between IVM, CQ, and HCQ arms in:
	  • Need for supplemental oxygen: 88% vs. 89% vs. 90%
	  • ICU admission: 28% vs. 22% vs. 21%
	  • Need for MV: 24% vs. 21% vs. 21%
	  • Mortality: 23% vs. 21% vs. 22%
	  • Mean number of days of supplemental oxygen: 8 days for each arm
	• Occurrence of AEs: no difference between arms
	• Baseline characteristics significantly associated with mortality:
	  • Aged >60 years (HR 2.4)
	  • DM (HR 1.9)
	  • BMI >33 (HR 2.0)
	  • SpO_2 <90% (HR 5.8)
		Key Limitations:
		• Small sample size
		• No clearly defined primary endpoint
		Interpretation:
		• Compared to CQ or HCQ, IVM did not reduce the proportion of hospitalized patients with severe COVID-19 who died or who required supplemental oxygen, ICU admission, or MV.

Key: AE = adverse event; ALT = alanine aminotransferase; BMI = body mass index; CNS = central nervous system; CQ = chloroquine; CrCl = creatinine clearance; CT = computed tomography; CXR = chest X-ray; DM = diabetes mellitus; HCQ = hydroxychloroquine; HTN = hypertension; ICU = intensive care unit; ITT = intention-to-treat; IVM = ivermectin; LOS = length of stay; MI = myocardial infarction; mITT = modified intention-to-treat; MV = mechanical ventilation; the Panel = the COVID-19 Treatment Guidelines Panel; PaO_2/FiO_2 = ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; PO = orally; RCT = randomized controlled trial; RDV = remdesivir; RT-PCR = reverse transcriptase polymerase chain reaction; SAE = severe adverse event; SOC = standard of care; SpO_2 = oxygen saturation; ULN = upper limit of normal; VL = viral load

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Lopinavir/Ritonavir and Other HIV Protease Inhibitors

Last Updated: February 11, 2021

The replication of 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.

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]

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- 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

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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%.

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- 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

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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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Nitazoxanide

Last Updated: July 8, 2021

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

Recommendation

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

Rationale

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

Please see Table 2e for more information.

Monitoring, Adverse Effects, and Drug-Drug Interactions

- Nitazoxanide is generally well tolerated. The most commonly reported side effects include abdominal pain, diarrhea, headache, nausea, vomiting, urine discoloration, and, rarely, ocular discoloration.
- Nitazoxanide is a highly plasma protein-bound drug (>99.9%). Drug-drug interactions may occur when nitazoxanide is administered concurrently with other highly plasma protein-bound drugs due to competition for binding sites. If nitazoxanide is coadministered with other highly protein-bound drugs with narrow therapeutic indices, monitor the patient for adverse drug reactions.
- Please see Table 2f for more information.

Considerations in Pregnancy

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

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Considerations in Children

Nitazoxanide is approved by the FDA for use in children aged ≥1 year old to treat *Cryptosporidium parvum* and *Giardia duodenalis* infections. Dosing for the nitazoxanide suspension or tablets is available for children that provides exposure that is similar to the approved adult dose of oral nitazoxanide 500 mg twice daily. There are no data on using nitazoxanide to treat COVID-19 in children.

Clinical Trials

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

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Table 2e. Nitazoxanide: 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 NTZ for the treatment of COVID-19. The clinical trials described in this table do not represent all the trials that the Panel reviewed while developing recommendations for NTZ.[1,2]

Study Design	Methods	Results	Limitations and Interpretation
Early Treatment of Mild COVID-19 with Nitazoxanide[3]			

Randomized, double-blind, placebo-controlled trial in nonhospitalized adults with mild COVID-19 in Brazil (n = 475)	**Key Inclusion Criteria:**
	• Clinical signs and symptoms of COVID-19 for ≤3 days (fever, dry cough, and/or fatigue)
	Key Exclusion Criteria:
	• Negative SARS-CoV-2 RT-PCR result from an NP swab
	• Renal, heart, respiratory, liver, or autoimmune diseases
	• Participant had a history of cancer in the past 5 years
	Interventions:
	• NTZ 500 mg 3 times daily for 5 days using the oral liquid formulation
	• Color-matched placebo 3 times daily for 5 days
	Primary Endpoint:
	• Complete resolution of dry cough, fever, and/or fatigue after receiving treatment for 5 days
	Key Secondary Endpoints:
	• Reduction in SARS-CoV-2 VL
	• Incidence of hospital admission after completing therapy
		Number of Participants:
		• NTZ (n = 194) and placebo (n = 198)
		Participant Characteristics:
		• Median age of patients was 37 years.
		  • Percentage of patients aged 18–39 years: 58%
		  • Percentage of patients aged 40–59 years: 36%
		  • Percentage of patients aged 60–77 years: 6%
		• 53% of patients were women.
		• 69% of patients were White.
		• 31% of patients had a BMI ≥30.
		• 85% of patients had no reported comorbidities.
		• Median time from symptom onset to first dose of study drug was 5 days (IQR 4–5 days).
		• Baseline median SARS-CoV-2 VL was 7.06 $\log_{10}$ c/mL (IQR 5.77–8.13) in NTZ arm and 7.49 $\log_{10}$ c/mL (IQR 6.15–8.32) in placebo arm ($P = 0.065$).
		Primary Outcome:
		• There was no difference in time to complete resolution of symptoms between NTZ and placebo arms ($P = 0.277$)
		Secondary Outcomes:
		• After 5 days, median SARS-CoV-2 VL was lower in NTZ arm (3.63 $\log_{10}$ c/mL [IQR 0–5.03]) than in placebo arm (4.13 $\log_{10}$ c/mL [IQR 2.88–5.31]; $P = 0.006$).
			Key Limitations:
			• In general, the patients in this study were young and relatively healthy.
			• At baseline, the median VL was 0.43 $\log_{10}$ c/mL lower in the NTZ arm than in the placebo arm; however, this difference was not statistically significant (trend toward a significant difference; $P = 0.065$). Although the difference in absolute VLs between the arms at Day 5 was reported as statistically significant, without the information on the change in VL in each arm, it is difficult to interpret the significance of the findings.
			• Some participants who received the study drug were excluded from the analysis population due to discontinued intervention (21 in NTZ arm vs. 18 in placebo arm); AEs (6 in NTZ arm vs. 1 in placebo arm); hospitalization (5 in NTZ arm vs. 5 in placebo arm); and protocol deviations (7 in NTZ arm vs. 7 in placebo arm). This complicates the interpretation of the study results, because an ITT analysis was not included.

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Study Design	Methods	Results	Limitations and Interpretation
Early Treatment of Mild COVID-19 with Nitazoxanide[3], continued			
		• 29.9% of patients in NTZ arm and 18.2% of patients in placebo arm had a negative SARS-CoV-2 RT-PCR result at the fifth treatment visit ($P = 0.009$). • In the ITT study population, 5 patients on NTZ and 5 on placebo were hospitalized due to clinical deterioration; 2 who received NTZ required ICU admission vs. 0 who received placebo. These individuals were excluded from the analysis population because they did not complete the 5-day treatment course before clinical progression occurred. **Other Outcomes:** • Mild to moderate AEs occurred in about 30% of participants in each arm who completed 5 days of therapy.	**Interpretation:** • NTZ did not improve time to resolution of symptoms compared to placebo. • Median VL was lower at Day 5 in the NTZ arm than in the placebo arm, but this may reflect differences in baseline VLs. • NTZ was well tolerated.
Early Treatment of Mild to Moderate COVID-19 with an Investigational Formulation of Nitazoxanide[4]			
Randomized, double-blind, placebo-controlled trial in nonhospitalized patients with COVID-19 in the United States and Puerto Rico (n = 1,092) *This is a preliminary, unpublished report that has not been peer reviewed.*	**Key Inclusion Criteria:** • Aged ≥12 years • Enrollment ≤72 hours of symptom onset • Mild to moderate COVID-19 • ≥2 respiratory symptom domains with a score ≥2 on FLU-PRO questionnaire at screening, and no improvement in overall symptom severity compared to previous day **Key Exclusion Criteria:** • Signs or symptoms of severe COVID-19 • Previous COVID-19 or any symptom suggestive of COVID-19 • Recent acute upper respiratory tract infection • Severe immunodeficiency • Severe heart, lung, neurological, or other systemic diseases	**Number of Participants:** • mITT analysis: NTZ (n = 184) and placebo (n = 195) **Participant Characteristics:** • Median age of patients was 40 years. • 43.5% of patients were men. • 87.6% of patients were White. • Median BMI was 28.9. • Median time from symptom onset to randomization was 45.9 hours. • 64.8% of patients had mild disease. • 35.2% of patients had moderate disease. • 62.8% of patients were at risk for severe illness. **Primary Outcome:** • NTZ was not associated with a reduction in median time to sustained response compared to placebo (13.3 days in NTZ arm vs. 12.4 days in placebo arm; $P = 0.88$) **Secondary Outcomes:** • Progression to severe disease occurred in 1 of 184 patients (0.5%) in NTZ arm and 7 of 195 patients (3.6%) in placebo arm ($P = 0.07$).	**Key Limitations:** • Information is limited in this preliminary report. • Because the number of high-risk participants who progressed to severe COVID-19 in this study was small, the results for this subgroup are fragile. Larger studies are needed. **Interpretation:** • NTZ did not demonstrate significant clinical or virologic benefits when compared to placebo. • NTZ was well tolerated.

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

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

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Table 2f. Characteristics of Antiviral Agents

Last Updated: May 31, 2022

- RDV is the only antiviral drug that is approved by the FDA for the treatment of COVID-19.
- RTV-boosted nirmatrelvir, MOV, and certain anti-SARS-CoV-2 mAbs have received EUAs from the FDA for the treatment of COVID-19.
- Other medications that are currently being evaluated in clinical trials for the treatment of COVID-19 are also included in this table. **The inclusion of these drugs does not imply that the Panel recommends their use.**
- This table focuses on small-molecule antiviral drugs. For more information regarding anti-SARS-CoV-2 mAbs, please see Table 3c.
- Information on CQ, HCQ, and LPV/RTV are available in archived versions of the Guidelines. The Panel **recommends against** using these agents to treat COVID-19.
- For many of these antiviral drugs, 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 or EUAs, when available.
- For drug interaction information, please refer to product labels, EUA fact sheets, and the Liverpool COVID-19 Drug Interactions website.
- For the Panel's recommendations on using the drugs listed in this table, please refer to the individual drug sections, Therapeutic Management of Nonhospitalized Adults With COVID-19, Therapeutic Management of Hospitalized Adults With COVID-19, or Antiviral Therapy Summary Recommendations.

Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Ritonavir-Boosted Nirmatrelvir (Paxlovid) *Authorized under FDA EUA for the treatment of mild to moderate COVID-19 in high-risk individuals aged ≥12 years and weighing ≥40 kg.*				
FDA EUA Doses for COVID-19[1] *Doses Based on eGFR:* • ≥60 mL/min: nirmatrelvir 300 mg (two, 150-mg tablets) with RTV 100 mg (one, 100-mg tablet) twice daily for 5 days • ≥30 to 60 mL/min: nirmatrelvir 150 mg (one, 150-mg tablet) with RTV 100 mg (one, 100-mg tablet) twice daily for 5 days • <30 mL/min: **not recommended**	• Dysgeusia • Diarrhea • HTN • Myalgia	• Monitor for potential AEs due to drug-drug interactions with concomitant medications. • Use with caution in patients with pre-existing liver diseases, liver enzyme abnormalities, or hepatitis. • Consider checking renal function in patients with suspected renal impairment.	• RTV-boosted nirmatrelvir has significant and complex drug-drug interactions. Before prescribing RTV-boosted nirmatrelvir, **carefully review concomitant medications**, including OTC medicines, herbal supplements, and recreational drugs. • See Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications	• Both nirmatrelvir and RTV tablets can be taken with or without food. • A list of clinical trials is available: Ritonavir-Boosted Nirmatrelvir

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Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Ritonavir-Boosted Nirmatrelvir (Paxlovid), continued				
Dosing for Patients with Severe Hepatic Impairment (Child-Pugh Class C): • **Not recommended**			for additional guidance and resources to assist with identifying drug-drug interactions.	
Remdesivir *Approved by the FDA for the treatment of COVID-19 in individuals aged ≥28 days and weighing ≥3 kg.*				
Dose for Adults and Children Weighing ≥40 kg: • RDV 200 mg IV on Day 1, then RDV 100 mg IV once daily from Day 2 **Dose for Children Aged ≥28 Days Weighing 3 kg to <40 kg:** • RDV 5 mg/kg IV on Day 1, then RDV 2.5 mg/kg IV once daily from Day 2 **Total Treatment Duration:** • Nonhospitalized patients: 3 days • Hospitalized patients: 5 days or until hospital discharge	• Nausea • ALT and AST elevations • Hypersensitivity • Increases in prothrombin time • Drug vehicle is SBECD, which has been associated with renal and liver 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. • Clinicians may consider preferentially using the lyophilized powder formulation (which contains less SBECD) in patients with renal impairment.	• Monitor patients for infusion reactions during the infusion and observe them for ≥1 hour after the infusion as clinically appropriate. • Monitor renal function, hepatic function and prothrombin time as clinically indicated. • The FDA does not recommend using RDV when eGFR is <30 mL/min. See Remdesivir for information on using RDV in people with renal insufficiency.	• Clinical drug-drug interaction studies of RDV have not been conducted. • In vitro, RDV is a minor substrate of CYP3A4, a substrate of OATP1B1 and P-gp, and an inhibitor of CYP3A4, OATP1B1, OATP1B3, and MATE1.[2]	• RDV should be administered in settings in which health care providers have immediate access to medications to treat severe infusion-related reactions or HSRs, such as anaphylaxis, and the ability to activate the emergency medical system. • A list of clinical trials is available: Remdesivir

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Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Molnupiravir *Authorized under FDA EUA for the treatment of mild to moderate COVID-19 in high-risk individuals aged ≥18 years.*				
Dose Recommended in FDA EUA: • MOV 800 mg (four, 200-mg capsules) PO every 12 hours for 5 days	• Diarrhea • Nausea • Dizziness • Per the FDA, the 5-day course of MOV has a low risk for genotoxicity.[3] See Molnupiravir for details.	• Before initiating MOV, assess pregnancy status as clinically indicated. • Monitor for potential AEs.	• Clinical drug-drug interaction studies of MOV have not been conducted. • Drug-drug interactions related to hepatic metabolism are not expected.	• MOV can be taken with or without food. • Sexually active individuals of reproductive potential should use effective contraception during and following treatment with MOV. See Molnupiravir for details. • If MOV is prescribed for a pregnant individual, the prescribing clinician should document that the risks and benefits were discussed and that the patient chose this therapy. Pregnant patients should also be informed of the pregnancy surveillance program and, if they agree to participate, be enrolled in the program. See Molnupiravir for details. • During MOV treatment and for 4 days after the final dose, lactating people **should not breastfeed** their infants. • MOV is not authorized for use in children aged <18 years due to potential effects on bone and cartilage growth. • A list of clinical trials is available: Molnupiravir

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Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Interferon Alfa *Not approved by the FDA and not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*				
IFN Alfa-2b *Dose for COVID-19 in Clinical Trials:* • Nebulized IFN alfa-2b 5 million international units twice daily; the optimal duration of treatment is unclear.	• AEs associated with inhaled therapy (e.g., throat irritation, cough, bronchospasm) • Minimal systemic effects expected	• Respiratory symptoms after inhalation	• Low potential for drug-drug interactions	• The nebulized formulation of IFN alfa has been the formulation most used in clinical trials for the treatment of COVID-19. IFN alfa is usually included as part of a combination regimen. • A list of clinical trials is available: Interferon Alfa **Availability:** • Nebulized IFN alfa-2b is not approved by the FDA for use in the United States.
Interferon Beta *Not approved by the FDA and not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*				
IFN Beta-1a *Dose for COVID-19 in Clinical Trials:* • IFN beta-1a 44 µg SUBQ or IV every other day for up to 3 or 4 doses **IFN Beta-1b** *Dose for COVID-19 in Clinical Trials:* • IFN beta-1b 8 million international units SUBQ every other day for up to 7 days total	• Flu-like symptoms (e.g., fever, fatigue, myalgia) • Leukopenia, neutropenia, thrombocytopenia, lymphopenia • Liver function abnormalities (ALT > AST) • Injection site reactions • Headache • Hypertonia • Pain • Rash • Worsening depression • Induction of autoimmunity	• CBC with differential • Liver enzymes • Worsening CHF • Depression, suicidal ideation	• Low potential for drug-drug interactions • **Use with caution** with other hepatotoxic agents. • Reduce dose if ALT >5 times ULN.	• A list of clinical trials is available: Interferon Beta **Availability** *Brand Names of IFN Beta-1a Products:* • Avonex, Plegridy, Rebif *Brand Names of IFN Beta-1b Products:* • Betaseron, Extavia

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Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Interferon Lambda *Not approved by the FDA and not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*				
PEG-IFN Lambda-1a *Dose for COVID-19 in Clinical Trials:* • Single dose of PEG-IFN lambda-1a 180 µg SUBQ	• Liver function abnormalities • Injection site reactions	• CBC with differential • Liver enzymes • Monitor for potential AEs.	• Low potential for drug-drug interactions • **Use with caution** with other hepatotoxic agents.	• A list of clinical trials is available: Interferon Lambda **Availability:** • PEG-IFN lambda-1a is not approved by the FDA for use in the United States.
Ivermectin *Not approved by the FDA and not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*				
Dose for COVID-19 in Clinical Trials: • IVM 200–600 µg/kg PO as a single dose or a once-daily dose for up to 5 days	• Dizziness • Pruritis • GI effects (e.g., nausea, diarrhea) • Neurological AEs have been reported when IVM has been used to treat 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	• Generally given on an empty stomach with water; however, administering IVM with food increases its bioavailability.[4] • A list of clinical trials is available: Ivermectin
Nitazoxanide *Not approved by the FDA and not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*				
Doses for Adults: • Doses studied for COVID-19 range from NTZ 500 mg PO 3 times daily to 4 times daily. • Higher doses are being studied. • Doses used for antiprotozoal indications range from NTZ 500 mg–1 g PO twice daily.	• Abdominal pain • Diarrhea • Headache • Nausea • Vomiting • Urine discoloration • Ocular discoloration (rare)	• Monitor for potential AEs.	• Drug-drug interactions may occur if NTZ is administered concurrently with other highly plasma protein-bound drugs due to competition for binding sites.[5] • If NTZ is coadministered with other highly protein-bound drugs with narrow therapeutic indices, monitor the patient for AEs.	• NTZ should be taken with food. • The oral suspension is not bioequivalent to the tablet formulation. • A list of clinical trials is available: Nitazoxanide

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Key: AE = adverse event; ALT = alanine transaminase; AST = aspartate aminotransferase; CBC = complete blood count; CHF = congestive heart failure; CQ = chloroquine; CYP = cytochrome P450; eGFR = estimated glomerular filtration rate; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; GI = gastrointestinal; HCQ = hydroxychloroquine; HSR = hypersensitivity reaction; HTN = hypertension; IFN = interferon; IV = intravenous; IVM = ivermectin; LPV/RTV = lopinavir/ritonavir; mAb = monoclonal antibody; MATE = multidrug and toxin extrusion protein; MOV = molnupiravir; NTZ = nitazoxanide; OATP = organic anion transporting polypeptide; OTC = over the counter; the Panel = the COVID-19 Treatment Guidelines Panel; PEG-IFN = pegylated interferon; P-gp = P-glycoprotein; PO = orally; RDV = remdesivir; RTV = ritonavir; SBECD = sulfobutylether-beta-cyclodextrin; SUBQ = subcutaneous; ULN = upper limit of normal

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Anti-SARS-CoV-2 Antibody Products

Last Updated: April 29, 2022

Summary Recommendations

The COVID-19 Treatment Guidelines Panel's (the Panel) recommendations for the use of anti-SARS-CoV-2 monoclonal antibodies (mAbs) are based on current knowledge of the in vitro activities of available products against the circulating SARS-CoV-2 variants and subvariants. These recommendations remain fluid and depend on the prevalence of resistant variants.

Anti-SARS-CoV-2 Monoclonal Antibodies for the Treatment of COVID-19

- Treatment with anti-SARS-CoV-2 mAbs should be considered for patients with mild to moderate COVID-19 who are hospitalized for a reason other than COVID-19 if they otherwise meet the Food and Drug Administration (FDA) Emergency Use Authorization (EUA) criteria for outpatient treatment.
- The risk for progression to severe COVID-19 in high-risk patients is substantially greater for those who are not vaccinated or those who are vaccinated but not expected to mount an adequate immune response to the vaccine due to an underlying immunocompromising condition. When the available therapies cannot be offered to all eligible patients, see Prioritization of Anti-SARS-CoV-2 Therapies for the Treatment and Prevention of COVID-19 When There Are Logistical or Supply Constraints for the Panel's recommendations.
- At this time, the Panel's anti-SARS-CoV-2 mAb recommendations are for the treatment of nonhospitalized patients with mild to moderate COVID-19 who are at high risk of progressing to severe disease.

Bebtelovimab

- The Panel recommends using **bebtelovimab 175 mg** intravenous injection in patients aged ≥12 years as an alternative therapy **ONLY** when ritonavir-boosted nirmatrelvir (Paxlovid) and remdesivir are not available, feasible to use, or clinically appropriate **(CIII)**. Treatment should be initiated as soon as possible and within 7 days of symptom onset. See Therapeutic Management of Nonhospitalized Adults With COVID-19 for further guidance.
- Bebtelovimab should be administered in a setting where severe hypersensitivity reactions, such as anaphylaxis, can be managed. Patients should be monitored during the injection and observed for at least 1 hour after injection.

Bamlanivimab Plus Etesevimab, Casirivimab Plus Imdevimab, and Sotrovimab

- Because the Omicron (B.1.1.529) variant of concern (VOC) and its subvariants have become dominant in the United States, the Panel **recommends against** using **bamlanivimab plus etesevimab**, **casirivimab plus imdevimab**, or **sotrovimab** for the treatment of COVID-19 **(AIII)**.

Anti-SARS-CoV-2 Monoclonal Antibodies as Post-Exposure Prophylaxis for SARS-CoV-2 Infection

- The Panel **recommends against** the use of **bamlanivimab plus etesevimab** and **casirivimab plus imdevimab** for SARS-CoV-2 post-exposure prophylaxis (PEP), as the Omicron VOC, which is not susceptible to these agents, is currently the dominant SARS-CoV-2 variant circulating in the United States **(AIII)**.

Anti-SARS-CoV-2 Monoclonal Antibodies as Pre-Exposure Prophylaxis for SARS-CoV-2 Infection

- The Panel recommends using **tixagevimab 300 mg plus cilgavimab 300 mg (Evusheld)** administered as 2 consecutive 3-mL intramuscular injections **(BIII)** as SARS-CoV-2 pre-exposure prophylaxis (PrEP) for adults and adolescents (aged ≥12 years and weighing ≥40 kg) who do not have SARS-CoV-2 infection, who have not been recently exposed to an individual with SARS-CoV-2 infection, **AND** who:
  - Are moderately to severely immunocompromised and may have an inadequate immune response to COVID-19 vaccination; *or*
  - Are not able to be fully vaccinated with any available COVID-19 vaccines due to a history of severe adverse reactions to a COVID-19 vaccine or any of its components.
- For individuals who previously received a dose of tixagevimab 150 mg plus cilgavimab 150 mg, the FDA EUA states that a second dose should be administered as soon as possible:
  - If the initial dose was administered ≤3 months ago, the second dose should be tixagevimab 150 mg plus cilgavimab 150 mg.
  - If the initial dose was administered >3 months ago, the second dose should be tixagevimab 300 mg plus cilgavimab 300 mg.

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Summary Recommendations, continued
• **Tixagevimab plus cilgavimab is not a substitute for COVID-19 vaccination and should not be used in unvaccinated individuals for whom COVID-19 vaccination is recommended and who are anticipated to have an adequate response.** • If supplies of tixagevimab plus cilgavimab are limited, priority for use as PrEP should be given to those who are at the highest risk for severe COVID-19 (see Prioritization of Anti-SARS-CoV-2 Therapies for the Treatment and Prevention of COVID-19 When There Are Logistical or Supply Constraints). **COVID-19 Convalescent Plasma** • The Panel **recommends against** the use of COVID-19 convalescent plasma (CCP) that was collected prior to the emergence of the Omicron VOC for the treatment of COVID-19 **(AIII)**. • The Panel **recommends against** the use of CCP for the treatment of COVID-19 in hospitalized, immunocompetent patients **(AI)**. • There is insufficient evidence for the Panel to recommend either for or against the use of high-titer CCP that was collected after the emergence of the Omicron VOC for the treatment of immunocompromised patients and nonhospitalized, immunocompetent patients with COVID-19. **Anti-SARS-CoV-2-Specific Immunoglobulins** • There is insufficient evidence for the Panel to recommend either for or against the use of anti-SARS-CoV-2-specific immunoglobulins for the treatment of COVID-19.
Rating of Recommendations: A = Strong; B = Moderate; C = Weak **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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Anti-SARS-CoV-2 Monoclonal Antibodies

Last Updated: April 29, 2022

The SARS-CoV-2 genome encodes 4 major structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N), as well as nonstructural and accessory proteins. The spike protein is further divided into 2 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 that results in virus-host cell membrane fusion and viral entry.[1] Anti-SARS-CoV-2 monoclonal antibodies (mAbs) that target the spike protein have been shown to have clinical benefits in treating SARS-CoV-2 infection. The effectiveness of the different anti-SARS-CoV-2 mAb therapies varies dramatically depending on the circulating variant, and the role of each anti-SARS-CoV-2 mAb in the treatment of COVID-19 remains fluid. The recommendations and discussion below pertain only to the use of the authorized anti-SARS-CoV-2 mAb products for the treatment of COVID-19. Currently, no product is available for post-exposure prophylaxis (PEP). For recommendations and discussion regarding the use of tixagevimab plus cilgavimab (Evusheld) as pre-exposure prophylaxis (PrEP), see Prevention of SARS-CoV-2 Infection.

The Omicron (B.1.1.529) variant of concern (VOC) has become the dominant SARS-CoV-2 variant in the United States.[2] This variant, which includes numerous mutations in the spike protein, has markedly reduced in vitro susceptibility to several anti-SARS-CoV-2 mAbs, especially bamlanivimab plus etesevimab and casirivimab plus imdevimab (REGEN-COV). Sotrovimab is active against the Omicron BA.1 and BA.1.1 subvariants, but it has substantially decreased in vitro activity against the Omicron BA.2 subvariant. Bebtelovimab retains in vitro activity against circulating Omicron subvariants.

Recommendations

The COVID-19 Treatment Guidelines Panel's (the Panel) recommendations for the use of anti-SARS-CoV-2 mAbs are based on current knowledge of the in vitro activities of the available products against the circulating SARS-CoV-2 variants and subvariants. These recommendations remain fluid and depend on the prevalence of resistant variants. At this time, the Panel's anti-SARS-CoV-2 mAb recommendations are for the treatment of nonhospitalized patients with mild to moderate COVID-19 who are at high risk of progressing to severe disease.

Bebtelovimab

The Panel recommends using **bebtelovimab** 175 mg intravenous (IV) injection in patients aged ≥12 years as an alternative therapy **ONLY** when ritonavir-boosted nirmatrelvir (Paxlovid) and remdesivir are not available, feasible to use, or clinically appropriate **(CIII)**. Treatment should be initiated as soon as possible and within 7 days of symptom onset. See Therapeutic Management of Nonhospitalized Adults With COVID-19 for further guidance.

Bamlanivimab Plus Etesevimab, Casirivimab Plus Imdevimab, and Sotrovimab

Because the Omicron VOC has become the dominant variant in the United States, the Panel **recommends against** using **bamlanivimab plus etesevimab**, **casirivimab plus imdevimab**, or **sotrovimab** for the treatment of COVID-19 **(AIII)**.

Additional Considerations

- Treatment with anti-SARS-CoV-2 mAbs should be started as soon as possible after SARS-CoV-2 infection is confirmed by an antigen test or a nucleic acid amplification test and within 7 days of

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symptom onset.

- Anti-SARS-CoV-2 mAbs should be administered in a setting where severe hypersensitivity reactions, such as anaphylaxis, can be managed. Patients should be monitored during the infusion and observed for at least 1 hour after infusion.
- Treatment with anti-SARS-CoV-2 mAbs should be considered for patients with mild to moderate COVID-19 who are hospitalized for a reason other than COVID-19 if they otherwise meet the Emergency Use Authorization (EUA) criteria for outpatient treatment.
  - The risk for progression to severe COVID-19 in high-risk patients is substantially greater for those who are not vaccinated or those who are vaccinated but not expected to mount an adequate immune response to the vaccine due to an underlying immunocompromising condition. When the available therapies cannot be offered to all eligible patients, see Prioritization of Anti-SARS-CoV-2 Therapies for the Treatment and Prevention of COVID-19 When There Are Logistical or Supply Constraints for the Panel's recommendations.
- There are no data on the combined use of antiviral agents and anti-SARS-CoV-2 mAbs for the treatment of nonhospitalized patients with COVID-19. Clinical trials are needed to determine whether this combination therapy has a role in the treatment of COVID-19.
- Severely immunocompromised patients may have prolonged SARS-CoV-2 replication, leading to more rapid viral evolution. There is a concern that using a single anti-SARS-CoV-2 mAb in these patients may result in emergence of resistant virus. Additional studies are needed to assess this risk. The role of anti-SARS-CoV-2 mAbs plus antiviral therapy in the treatment of COVID-19 is not yet known.[3,4]

Anti-SARS-CoV-2 Monoclonal Antibodies That Have Received Emergency Use Authorizations

Five anti-SARS-CoV-2 mAb products have received EUAs from the Food and Drug Administration (FDA). Bamlanivimab plus etesevimab, bebtelovimab, casirivimab plus imdevimab, and sotrovimab received EUAs for the treatment of mild to moderate COVID-19 in nonhospitalized patients with laboratory-confirmed SARS-CoV-2 infection who are at high risk for progressing to severe disease or hospitalization. The FDA issued an EUA for tixagevimab plus cilgavimab, a long-acting anti-SARS-CoV-2 mAb combination, as SARS-CoV-2 PrEP for individuals who do not have SARS-CoV-2 infection, who have not been recently exposed to an individual with SARS-CoV-2 infection, **AND** who are at risk for inadequate immune response to COVID-19 vaccination **OR** have a documented history of severe adverse reactions to a COVID-19 vaccine or any of its components (see Prevention of SARS-CoV-2 Infection for more information). The issuance of an EUA does not constitute FDA approval.

The authorized anti-SARS-CoV-2 mAb products, listed alphabetically, are:

- *Bamlanivimab plus etesevimab:* These neutralizing mAbs bind to different, but overlapping, epitopes in the spike protein RBD of SARS-CoV-2.
  - The distribution of bamlanivimab plus etesevimab has paused in the United States because the Omicron VOC has markedly reduced in vitro susceptibility to bamlanivimab and etesevimab; therefore, this regimen is not expected to provide clinical benefit for patients with Omicron infection.[5]
- *Bebtelovimab:* This recombinant neutralizing human mAb binds to the spike protein of SARS-CoV-2. Bebtelovimab retains in vitro activity against all circulating Omicron subvariants, but there are no clinical efficacy data on the treatment of patients at high risk for progression to

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severe COVID-19.[6]

- *Casirivimab plus imdevimab:* These recombinant human mAbs bind to nonoverlapping epitopes of the spike protein RBD of SARS-CoV-2.
  - The distribution of casirivimab plus imdevimab has paused in the United States because the Omicron VOC has markedly reduced in vitro susceptibility to casirivimab and imdevimab; therefore, this regimen is not expected to provide clinical benefit for patients with Omicron infection.[7]
- *Sotrovimab:* This mAb was originally identified in 2003 from a survivor of SARS-CoV infection. It targets an epitope in the RBD of the spike protein that is conserved between SARS-CoV and SARS-CoV-2. Sotrovimab retains in vitro activity against the Omicron BA.1 and BA.1.1 subvariants, but it has substantially decreased in vitro activity against Omicron BA.2 and is not expected to provide clinical benefit for patients with Omicron BA.2 infection.[8-10]
  - Because the Omicron BA.2 subvariant is now the dominant circulating subvariant in all regions of the United States, distribution of sotrovimab has paused, and the Panel no longer recommends using sotrovimab for the treatment of COVID-19.
- *Tixagevimab plus cilgavimab:* These recombinant human anti-SARS-CoV-2 mAbs bind to nonoverlapping epitopes of the spike protein RBD of SARS-CoV-2. The originally authorized dose of tixagevimab 150 mg plus cilgavimab 150 mg has reduced in vitro activity against the Omicron BA.1 and BA.1.1 subvariants. However, the FDA updated the EUA to authorize a dose of tixagevimab 300 mg plus cilgavimab 300 mg, which is expected to maintain activity against these subvariants. Tixagevimab plus cilgavimab has retained in vitro activity against the Omicron BA.2 subvariant.[11-13]

SARS-CoV-2 Variant Susceptibility to Anti-SARS-CoV-2 Monoclonal Antibodies

In laboratory studies, some SARS-CoV-2 variants that harbor certain mutations have markedly reduced susceptibility to several of the authorized anti-SARS-CoV-2 mAbs (see Table A).[14] The clinical relevance of the reduced in vitro susceptibility of select variants to anti-SARS-CoV-2 mAbs is under investigation.

Some key SARS-CoV-2 variants that have been identified are:

- *Alpha (B.1.1.7):* This variant retains in vitro susceptibility to all anti-SARS-CoV-2 mAb products currently available through FDA EUAs.[15-17]
- *Beta (B.1.351):* This variant has markedly reduced in vitro susceptibility to bamlanivimab and etesevimab.[15,17] In vitro studies also suggest that the Beta variant has markedly reduced susceptibility to casirivimab; however, the combination of casirivimab and imdevimab appears to retain activity against the variant.[16] Sotrovimab also appears to retain activity against the variant.[8]
- *Gamma (P.1):* This variant has markedly reduced in vitro susceptibility to bamlanivimab and etesevimab.[15,18] The Gamma variant also has reduced susceptibility to casirivimab; however, the combination of casirivimab plus imdevimab appears to retain activity against the variant.[16] Sotrovimab also appears to retain activity against the Gamma variant.[8]
- *Delta (B.1.617.2, non-AY.1/AY.2):* This VOC retains in vitro susceptibility to all anti-SARS-CoV-2 mAbs currently available through FDA EUAs.[15,16]
- *Omicron (B.1.1.529):* This is currently the predominant VOC circulating in the United States and includes the BA.1, BA.1.1, and BA.2 subvariants. This variant, which includes numerous mutations in the spike protein, has markedly reduced in vitro susceptibility to some anti-SARS-CoV-2 mAb products, as noted below:

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- Bamlanivimab plus etesevimab and casirivimab plus imdevimab are not expected to be active against these subvariants.[12]
- Sotrovimab retains activity against the Omicron BA.1 and BA.1.1 subvariants but has decreased in vitro activity against the Omicron BA.2 subvariant.[8,12,13]
- Bebtelovimab retains in vitro activity against all circulating Omicron subvariants.[6,9,19]
- The originally authorized dose of tixagevimab 150 mg plus cilgavimab 150 mg has reduced in vitro activity against the Omicron BA.1 and BA.1.1 subvariants.[11] However, the FDA updated the EUA to authorize a dose of tixagevimab 300 mg plus cilgavimab 300 mg, which is expected to maintain activity against these subvariants. The duration of protection against the BA.1 and BA.1.1 subvariants remains unclear. Tixagevimab plus cilgavimab has retained in vitro activity against the Omicron BA.2 subvariant.[11-13,20]

To define the utility of specific mAbs in the future, ongoing population-based genomic surveillance of the types and proportions of circulating SARS-CoV-2 variants, as well as studies on the susceptibility of different variants to available anti-SARS-CoV-2 mAbs, will be important.

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Table A. SARS-CoV-2 Variants and Susceptibility to Anti-SARS-CoV-2 Monoclonal Antibodies

WHO Label	Pango Lineage	CDC Variant Class	Notable Mutations	BAM Plus ETE		CAS Plus IMD		BEB		SOT		TIX Plus CIL	
				In Vitro Suscept-ibility[a]	Anti-cipated Clinical Activity	In Vitro Suscept-ibility[a]	Anti-cipated Clinical Activity	In Vitro Suscept-ibility[a]	Anti-cipated Clinical Activity	In Vitro Suscept-ibility[a]	Anti-cipated Clinical Activity	In Vitro Suscept-ibility[a]	Anti-cipated Clinical Activity
Alpha	B.1.1.7	VBM	N501Y	No change	Active	No change	Active	No change	Active	No change	Active	No change	Active
Beta	B.1.351	VBM	K417N, E484K, N501Y	Marked reduction	Unlikely to be active	No change[b]	Active	No change	Active	No change	Active	No change	Active
Gamma	P.1	VBM	K417T, E484K, N501Y	Marked reduction	Unlikely to be active	No change[b]	Active	No change	Active	No change	Active	No change	Active
Delta	B.1.617.2, non-AY.1/ AY.2	VOC	L452R, T478K	No change	Active	No change	Active	No change	Active	No change	Active	No change	Active
Omicron	B.1.1.529/ BA.1	VOC	K417N, N440K, G446S, E484A, Q493R, N501Y	Marked reduction	Unlikely to be active	Marked reduction	Unlikely to be active	No change	Active	No change	Active	Moderate reduction[c]	Active[d]
Omicron	B.1.1.529/ BA.1.1	VOC	R346K, K417N, N440K, G446S, E484A, Q493R, N501Y	Marked reduction	Unlikely to be active	Marked reduction	Unlikely to be active	No change	Active	No change	Active	Moderate reduction[c]	Active[d]
Omicron	B.1.1.529/ BA.2	VOC	T376A, K417N, N440K, E484A, Q493R, N501Y	Marked reduction	Unlikely to be active	Marked reduction	Unlikely to be active	No change	Active	Marked reduction	Unlikely to be active	No change	Active

[a] Based on the fold reduction in susceptibility reported in the FDA EUAs.[8,11,15,16]

[b] Marked change for CAS and no change for IMD. The combination of CAS plus IMD appears to retain activity against the variant.

[c] Despite the moderately reduced in vitro susceptibility of TIX plus CIL, in vitro PK/PD modeling data suggest that the TIX 300 mg plus CIL 300 mg dose will retain

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activity against the Omicron VOC.[11]

[d] The duration of protection against SARS-CoV-2 infection remains unclear.

Key: BAM = bamlanivimab; BEB = bebtelovimab; CAS = casirivimab; CIL = cilgavimab; CDC = Centers for Disease Control and Prevention; ETE = etesevimab; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; IMD = imdevimab; PK/PD = pharmacokinetic/pharmacodynamic; SOT = sotrovimab; TIX = tixagevimab; VBM = variant being monitored; VOC = variant of concern; WHO = World Health Organization

Clinical Trials

In placebo-controlled, randomized trials in nonhospitalized patients with mild to moderate COVID-19 symptoms and certain risk factors for disease progression, the use of anti-SARS-CoV-2 mAb products reduced the risk of hospitalization and death (see Table 3a).[6,8,15,16] These studies were conducted before the widespread circulation of the Omicron VOC. The potential impact of this variant and its susceptibility to different FDA-authorized anti-SARS-CoV-2 mAbs are discussed below.

Bebtelovimab

Based on in vitro data, bebtelovimab is expected to have activity against a broad range of SARS-CoV-2 variants, including the Omicron VOC and its BA.1 and BA.2 subvariants.[6,9,19] The Panel's recommendation on bebtelovimab is primarily based on laboratory data showing its potent activity against the Omicron VOC (including the BA.1 and BA.2 subvariants) and other VOCs, as well as on limited clinical trial data from the Phase 2 BLAZE-4 study.[6]

The multi-armed, Phase 2 BLAZE-4 study included 1 small, placebo-controlled, randomized trial in patients at low risk of disease progression. It also included 1 small randomized controlled trial that compared bebtelovimab alone to an anti-SARS-CoV-2 mAb combination of bamlanivimab, etesevimab, and bebtelovimab in patients at high risk of disease progression (see Table 3a).[6] Among low-risk individuals, the mean decline in viral load at Day 5 was greater in the 2 bebtelovimab arms than in the placebo arm. The median time to sustained symptom resolution was 6 days in the bebtelovimab alone arm and 8 days in the placebo arm ($P = 0.003$).

Large randomized controlled trials are needed to fully evaluate the efficacy of bebtelovimab in a high-risk population. Nevertheless, when other therapeutic options are not available, feasible to use, or clinically appropriate, in vitro susceptibility data and the antiviral activity and clinical benefits observed in Phase 2 trials support the use of bebtelovimab for nonhospitalized patients with mild to moderate COVID-19 at high risk of progressing to severe COVID-19. In addition, bebtelovimab has mechanisms of action similar to those of other authorized anti-SARS-CoV-2 mAbs that have shown definitive clinical benefits in this population.

Bamlanivimab Plus Etesevimab

The distribution of bamlanivimab plus etesevimab has paused in the United States because the Omicron VOC and subvariants have markedly reduced in vitro susceptibility to this mAb regimen.[5] Prior to the spread of the Omicron variant, the Phase 3 BLAZE-1 trial had demonstrated a clinical benefit of bamlanivimab plus etesevimab in people with mild to moderate COVID-19 who are at high risk for progression to severe disease or hospitalization.[21]

Casirivimab Plus Imdevimab

The distribution of casirivimab plus imdevimab has paused in the United States because the Omicron VOC and subvariants have markedly reduced in vitro susceptibility to this mAb regimen.[7] Prior to the spread of the Omicron variant, the FDA had authorized the use of casirivimab 600 mg plus imdevimab 600 mg administered as a single IV infusion for the treatment of people with

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mild to moderate COVID-19 who are at high risk for progression to severe disease or hospitalization.[8] The recommendation for using the dose of casirivimab 600 mg plus imdevimab 600 mg IV is based on data from a Phase 3, double-blind, placebo-controlled, randomized trial demonstrating clinical benefit in outpatients with mild to moderate COVID-19. The FDA also authorized subcutaneous (SUBQ) injection of the regimen if an IV infusion is not feasible or would delay treatment. SUBQ administration of casirivimab plus imdevimab requires 4 injections (2.5 mL per injection) at 4 different sites (see the FDA EUA for details).

Sotrovimab

Sotrovimab retains in vitro activity against the Omicron BA.1 and BA.1.1 subvariants of the Omicron VOC, but it has substantially decreased in vitro activity against the Omicron BA.2 subvariant and is not expected to provide clinical benefit for patients with Omicron BA.2 infection.[8] Because the Omicron BA.2 subvariant is now the dominant circulating subvariant in all regions of the United States, distribution of sotrovimab has paused, and the Panel no longer recommends using sotrovimab to treat COVID-19.

Data that support the sotrovimab EUA are from the Phase 3 COMET-ICE trial, which included outpatients with mild to moderate COVID-19 who were at high risk for progression to severe disease or hospitalization. A total of 1,057 participants were randomized within 5 days of symptom onset to receive sotrovimab 500 mg IV (n = 528) or placebo (n = 529). The primary endpoint was the proportion of participants who were hospitalized for ≥24 hours or who died from any cause by Day 29. Endpoint events occurred in 6 of 528 participants (1%) in the sotrovimab arm and 30 of 529 participants (6%) in the placebo arm, resulting in a 4.53% absolute difference in the risk of hospitalization or death among those who received sotrovimab. The adjusted relative risk of hospitalization or death for those who received sotrovimab was 0.21.[8,22]

See Table 3a for more information on the clinical trials evaluating the safety and efficacy of anti-SARS-CoV-2 mAbs in patients with COVID-19.

Criteria for Use of Anti-SARS-CoV-2 Monoclonal Antibodies Under Emergency Use Authorizations

The FDA EUAs for anti-SARS-CoV-2 mAbs include a list of specific conditions that place patients at high risk for clinical progression. On May 14, 2021, the FDA revised the EUAs to broaden these criteria.[15,16] Notable changes included lowering the body mass index (BMI) cutoff from ≥35 to >25 and adding other conditions and factors (e.g., pregnancy, race or ethnicity). Other than being aged ≥12 years, there are no longer any age criteria restricting the use of these products in patients with the following conditions: sickle cell disease, neurodevelopmental disorders, medical-related technological dependence, asthma, cardiovascular disease, hypertension, and chronic lung disease.

For guidance when available therapies cannot be offered to all eligible patients, see Prioritization of Anti-SARS-CoV-2 Therapies for the Treatment and Prevention of COVID-19 When There Are Logistical or Supply Constraints.

Recommendations

The strength of the evidence for using anti-SARS-CoV-2 mAbs varies depending on the medical conditions and other factors that place patients at high risk for progression to severe COVID-19 or hospitalization. The ratings for the Panel's recommendations are based on FDA EUA criteria for identifying high-risk individuals.

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- For patients with high-risk conditions that have been represented in clinical trials evaluating anti-SARS-CoV-2 mAbs, the Panel recommends the use of anti-SARS-CoV-2 mAbs, with the following ratings:
  - Aged ≥65 years **(AIIa)**
  - Obesity (BMI >30) **(AIIa)**
  - Diabetes **(AIIa)**
  - Cardiovascular disease (including congenital heart disease) or hypertension **(AIIa)**
  - Chronic lung diseases (e.g., chronic obstructive pulmonary disease, moderate-to-severe asthma, interstitial lung disease, cystic fibrosis, pulmonary hypertension) **(AIIa)**
- For patients with conditions that have had limited representation in clinical trials but are considered a high risk for progression to severe COVID-19 by the Centers for Disease Control and Prevention (CDC), the Panel recommends the use of anti-SARS-CoV-2 mAbs, with the following ratings:
  - Immunocompromised or receiving immunosuppressive treatment **(AIII)**; many experts strongly recommend therapy for patients with these conditions, despite limited representation in clinical trials
  - Overweight (i.e., BMI 25–30) as a sole risk factor **(BIII)**
  - Chronic kidney disease **(BIII)**
  - Pregnancy **(BIII)**
  - Sickle cell disease **(BIII)**
  - Neurodevelopmental disorder (e.g., cerebral palsy) or another condition that confers medical complexity (e.g., genetic or metabolic syndromes, severe congenital anomalies) **(BIII)**
  - Medical-related technological dependence (e.g., tracheostomy, gastrostomy, positive pressure ventilation not related to COVID-19) **(BIII)**
  - Infants aged <1 year. Although **bamlanivimab plus etesevimab** is authorized for use in this high-risk group, the Panel **recommends against** using this mAb regimen **(AIII)** because it has markedly reduced activity against Omicron, the dominant VOC in the United States.

It is important to note that the likelihood of developing severe COVID-19 increases when a person has multiple high-risk conditions or comorbidities.[23-26] Medical conditions or other factors (e.g., race or ethnicity) that are not listed in the mAb EUAs may also be associated with high risk for progression to severe COVID-19. The current EUAs state that the use of anti-SARS-CoV-2 mAbs may be considered for patients with high-risk conditions and factors that are not listed in the EUAs. For additional information on medical conditions and other factors that are associated with an increased risk for progression to severe COVID-19, see the CDC webpage People With Certain Medical Conditions. The decision to use anti-SARS-CoV-2 mAbs for a patient should be based on an individualized assessment of risks and benefits.[8]

Using Anti-SARS-CoV-2 Monoclonal Antibodies in Patients Hospitalized for COVID-19

The anti-SARS-CoV-2 mAbs available through FDA EUAs are not authorized for use in the following patients:

- Those hospitalized for COVID-19; *or*

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- Those who require oxygen therapy or respiratory support due to COVID-19; *or*
- Those who are on chronic oxygen therapy due to an underlying non-COVID-19-related comorbidity and who require an increase in oxygen flow rate from baseline or respiratory support because of COVID-19.

The FDA EUAs do permit the use of anti-SARS-CoV-2 mAb products in patients who are hospitalized for a diagnosis other than COVID-19, provided they have mild to moderate COVID-19 and are at high risk for progressing to severe disease.[6,16,27,28]

Anti-SARS-CoV-2 mAbs have been evaluated in hospitalized patients with severe COVID-19. A substudy of the ACTIV-3/TICO trial randomized patients who were hospitalized for COVID-19 to receive bamlanivimab 7,000 mg or placebo, each in addition to remdesivir. On October 26, 2020, study enrollment was halted after a prespecified interim futility analysis indicated a lack of clinical benefit for bamlanivimab.[29,30]

Prior to the spread of the Omicron VOC, data supported the use of anti-SARS-CoV-2 mAbs in hospitalized patients with COVID-19 who are seronegative for the anti-spike protein antibody and/or have evidence of ongoing viral replication. In a subset analysis of the ACTIV-3 trial, 153 of 314 participants (49%) were negative for the anti-spike endogenous neutralizing antibody. The subhazard ratio (sHR) comparing bamlanivimab to placebo for sustained recovery (defined as discharge home and remaining at home for ≥14 days through Day 90) was 1.24 among the participants who were seronegative (CI, 0.90–1.70) versus 0.74 among those who were seropositive (CI, 0.54–1.00). Furthermore, the difference for sustained recovery between bamlanivimab and placebo was even greater among the seronegative participants who had high viral loads (sHR 1.89; CI, 1.23–2.91). However, these results are limited due to the trial's early termination for futility and small sample size.[31]

The ACTIV-3/TICO trial also randomized hospitalized patients with COVID-19 to receive sotrovimab 500 mg IV, an anti-SARS-CoV-2 mAb combination of BRII-196 1,000 mg IV plus BRII-198 1,000 mg IV, or placebo, each in addition to remdesivir. On March 1, 2021, study enrollment was halted after a prespecified interim futility analysis indicated a lack of clinical benefit for sotrovimab or BRII-196 plus BRII-198.[32] A subset analysis did not suggest efficacy for sotrovimab in those with or without endogenous antibodies.

In the RECOVERY study, hospitalized patients with COVID-19 were randomized to receive usual care with casirivimab 4,000 mg plus imdevimab 4,000 mg IV or usual care alone. There was no difference in 28-day all-cause mortality between the casirivimab plus imdevimab arm and the usual care arm; 943 of 4,839 patients (19%) in the casirivimab plus imdevimab arm died versus 1,029 of 4,946 patients (21%) in the usual care arm (rate ratio 0.94; 95% CI, 0.86–1.02; $P = 0.14$). However, in the subgroup of patients who were seronegative for the anti-spike protein antibody, there was a significant reduction in 28-day all-cause mortality in the casirivimab plus imdevimab arm (396 of 1,633 casirivimab plus imdevimab recipients [24%] died vs. 452 of 1,520 usual care recipients [30%]; rate ratio 0.79; 95% CI, 0.69–0.91; $P = 0.0009$).[33] Under the current EUA, this higher dose of casirivimab plus imdevimab is not available, and the lower dose is only authorized for use in nonhospitalized patients with COVID-19. In addition, rapid serology testing that can identify seronegative individuals in real time is currently not widely available.

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

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Monitoring

Bebtelovimab should be administered by IV injection and should **only be administered in health care settings** by qualified health care providers who have immediate access to emergency medical services and medications that treat severe infusion-related reactions. Patients should be monitored during the IV injection and for at least 1 hour after the injection is completed.

Adverse Effects

Hypersensitivity, including anaphylaxis and infusion-related reactions, has been reported in patients who received anti-SARS-CoV-2 mAbs. Rash, diarrhea, nausea, vomiting, dizziness, and pruritis have also been reported.[6,8,16,28]

Drug-Drug Interactions

Drug-drug interactions are unlikely between the authorized anti-SARS-CoV-2 mAbs and medications that are renally excreted or that are cytochrome P450 substrates, inhibitors, or inducers (see Table 3c).

Considerations in Pregnancy

The use of anti-SARS-CoV-2 mAbs can be considered for pregnant people with COVID-19, especially those who have additional risk factors for severe disease (see the EUA criteria for the use of these products above).

As immunoglobulin (Ig) G mAbs, the authorized anti-SARS-CoV-2 mAbs would be expected to cross the placenta. There are no pregnancy-specific data on the use of these mAbs; however, other IgG products have been safely used in pregnant people when their use is indicated. Therefore, authorized anti-SARS-CoV-2 mAbs should not be withheld during pregnancy. When possible, pregnant and lactating people should be included in clinical trials that are evaluating the use of anti-SARS-CoV-2 mAbs for the treatment or prevention of COVID-19.

Considerations in Children

Please see Special Considerations in Children for therapeutic recommendations for children with COVID-19.

Drug Availability

Bebtelovimab is currently being distributed to all regions without restriction. The broad distribution of bamlanivimab plus etesevimab, casirivimab plus imdevimab, and sotrovimab has paused in the United States because the Omicron VOC has reduced susceptibility to these anti-SARS-CoV-2 mAbs.[5,7]

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

Last Updated: April 29, 2022

This table describes only the clinical trials that have evaluated anti-SARS-CoV-2 mAbs for the treatment of COVID-19. Please see Prevention of SARS-CoV-2 Infection for a discussion of the clinical trials that have evaluated anti-SARS-CoV-2 mAbs for PEP of SARS-CoV-2 infection.

Methods	Results	Limitations and Interpretation
BLAZE-1: Double-Blind RCT of Bamlanivimab 700 mg Plus Etesevimab 1,400 mg in Nonhospitalized Patients With Mild to Moderate COVID-19 in the United States and Puerto Rico[1]		
Key Inclusion Criteria: • Aged ≥12 years • At high risk for severe COVID-19 or hospitalization **Interventions:** • Within 3 days of a positive SARS-CoV-2 test result, single infusion of: • BAM 700 mg plus ETE 1,400 mg (n = 511) • Placebo (n = 258) **Primary Endpoint:** • COVID-19-related hospitalization (defined as ≥24 hours of acute care) or death from any cause by Day 29	**Participant Characteristics:** • Median age 56 years; 30% aged ≥65 years; 53% women • 87% White, 27% Hispanic/Latinx, 8% Black/African American • Mean duration of symptoms was 4 days • 76% with mild COVID-19, 24% with moderate COVID-19 **Primary Outcomes:** • COVID-19-related hospitalizations or all-cause deaths by Day 29: 4 (0.8%) in BAM plus ETE arm vs. 15 (5.8%) in placebo arm (change of -5.0%; 95% CI, -8.0% to -2.1%; $P < 0.001$) • All-cause deaths by Day 29: 0 in BAM plus ETE arm vs. 4 (1.6%) in placebo arm	**Key Limitation:** • Conducted before widespread circulation of the Omicron VOC **Interpretation:** • Compared to placebo, BAM plus ETE significantly reduced the number of COVID-19-related hospitalizations and all-cause deaths in high-risk patients.
BLAZE-4, Treatment Arms 9–11: Double-Blind RCT of Bamlanivimab Plus Etesevimab Plus Bebtelovimab Versus Bebtelovimab Alone Versus Placebo in Low-Risk, Nonhospitalized Patients With Mild to Moderate COVID-19[2]		
Key Inclusion Criteria: • Aged 18–64 years • No risk factors for progression to severe COVID-19 **Key Exclusion Criteria:** • ≥1 of the following: • SpO_2 ≤93% on room air • Respiratory rate ≥30 breaths/min • Heart rate ≥125 bpm **Interventions:** • Within 3 days of a positive SARS-CoV-2 test result, single infusion of:	**Participant Characteristics:** • Median age 35 years; 56% women • 36% Hispanic/Latinx, 19% Black/African American • Mean duration of symptoms prior to enrollment was 3.6 days **Primary Outcomes:** • Proportion with PHVL: • 13% in BAM plus ETE plus BEB arm vs. 21% in placebo arm ($P = 0.098$), with a relative reduction of 38% (95% CI, -9% to 65%) • 14% in BEB arm vs. 21% in placebo arm ($P = 0.147$), with a relative reduction of 34% (95% CI, -15% to 62%)	**Key Limitations:** • Only low-risk patients included • Not powered to assess hospitalizations and deaths • Conducted before widespread circulation of the Omicron VOC **Interpretations:** • There were no differences in the proportion of patients with PHVL across the arms. • Few COVID-19-related hospitalizations or deaths from any

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Methods	Results	Limitations and Interpretation
BLAZE-4, Treatment Arms 9–11: Double-Blind RCT of Bamlanivimab Plus Etesevimab Plus Bebtelovimab Versus Bebtelovimab Alone Versus Placebo in Low-Risk, Nonhospitalized Patients With Mild to Moderate COVID-19[2], continued		
• BAM 700 mg plus ETE 1,400 mg plus BEB 175 mg (n = 127) • BEB 175 mg (n = 125) • Placebo (n = 128) **Primary Endpoint:** • Proportion of patients with PHVL (defined as SARS-CoV-2 VL >5.82 $\log_{10}$ by Day 7) **Key Secondary Endpoints:** • Mean change in VL from baseline to Days 3, 5, 7, and 11 • COVID-19-related hospitalization or death from any cause by Day 29 • Time to sustained symptom resolution	**Secondary Outcomes:** • Mean decline in VL greater in mAb arms vs. placebo arm at Day 5 but not at Days 3, 7, or 11 • COVID-19-related hospitalizations or all-cause deaths by Day 29: • 3 (2.4%) in BAM plus ETE plus BEB arm, including 1 death • 2 (1.6%) in BEB arm • 2 (1.6%) in placebo arm • Median time to sustained symptom resolution: • 7 days in BAM plus ETE plus BEB arm vs. 8 days in placebo arm (P = 0.289) • 6 days in BEB arm vs. 8 days in placebo arm (P = 0.003)	cause occurred by Day 29 across the arms, as is expected for a population of individuals who were at low risk of severe COVID-19. • Compared to placebo, the median time to sustained symptom resolution was shorter in the BEB arm.
BLAZE-4, Treatment Arms 12 and 13: Open-Label RCT of Bamlanivimab Plus Etesevimab Plus Bebtelovimab and Bebtelovimab Alone in High-Risk, Nonhospitalized Patients With Mild to Moderate COVID-19[2]		
Key Inclusion Criteria: • Aged ≥12 years • Weight ≥40 kg • ≥1 risk factor for progression to severe COVID-19 **Key Exclusion Criteria:** • ≥1 of the following: • SpO_2 ≤93% on room air • Respiratory rate ≥30 breaths/min • Heart rate ≥125 bpm **Interventions:** • Within 3 days of a positive SARS-CoV-2 test result, single infusion of: • BAM 700 mg plus ETE 1,400 mg plus BEB 175 mg (n = 50) • BEB 175 mg (n = 100)	**Participant Characteristics:** • Median age 50 years; 52% women • 18% Hispanic/Latinx, 18% Black/African American • Mean duration of symptoms prior to enrollment was 4.7 days • 21% had at least 1 dose of COVID-19 vaccine **Efficacy Outcomes:** • COVID-19-related hospitalization or death from any cause by Day 29: 2 (4%) in BAM plus ETE plus BEB arm vs. 3 (3%) in BEB arm • Mean decline in VL greater in BAM plus ETE plus BEB arm vs. BEB arm at Day 5 but not at Days 3, 7, or 11	**Key Limitations:** • Open-label study • No placebo arm • Not powered to assess hospitalizations and deaths • Conducted before widespread circulation of the Omicron VOC **Interpretation:** • There was no difference in the proportion of patients who were hospitalized or who died between the arms.

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Methods	Results	Limitations and Interpretation
BLAZE-4, Treatment Arms 12 and 13: Open-Label RCT of Bamlanivimab Plus Etesevimab Plus Bebtelovimab and Bebtelovimab Alone in High-Risk, Nonhospitalized Patients With Mild to Moderate COVID-19[2], continued		
Efficacy Endpoints: • COVID-19-related hospitalization or death from any cause by Day 29 • Mean change in VL from baseline to Days 3, 5, 7, and 11		
Double-Blind RCT of Casirivimab Plus Imdevimab in Nonhospitalized Patients With Mild to Moderate COVID-19[3]		

Key Inclusion Criteria:
• Aged ≥18 years
• Laboratory-confirmed SARS-CoV-2 infection
• Symptom onset within 7 days of randomization
• For patients included in the modified full analysis only:
  • ≥1 risk factor for severe COVID-19
  • Positive SARS-CoV-2 RT-PCR result at baseline
Interventions:
• Single IV infusion of:
  • CAS 600 mg plus IMD 600 mg (n = 736) or placebo (n = 748)
  • CAS 1,200 mg plus IMD 1,200 mg (n = 1,355) or placebo (n = 1,341)
Primary Endpoint:
• ≥1 COVID-19-related hospitalization or death from any cause by Day 29
	Participant Characteristics:
	• Median age 50 years
	• 35% Hispanic/Latinx, 5% Black/African American
	• Median duration of symptoms prior to enrollment was 3 days
	Primary Outcomes:
	• COVID-19-related hospitalizations or all-cause deaths through Day 29:
	  • 7 (1.0%) in CAS 600 mg plus IMD 600 mg arm vs. 24 (3.2%) in placebo arm ($P = 0.002$)
	  • 18 (1.3%) in CAS 1,200 mg plus IMD 1,200 mg arm vs. 62 (4.6%) in placebo arm ($P < 0.001$)
	• All-cause deaths:
	  • 1 (0.1%) in CAS 600 mg plus IMD 600 mg arm vs. 1 (0.1%) in placebo arm
	  • 1 (< 0.1%) in CAS 1,200 mg plus IMD 1,200 mg arm vs. 3 (0.2%) in placebo arm
		Key Limitation:
		• Conducted before widespread circulation of the Omicron VOC
		Interpretation:
		• Compared to placebo, CAS 600 mg plus IMD 600 mg and CAS 1,200 mg plus IMD 1,200 mg reduced the risk of COVID-19-related hospitalizations or all-cause deaths in patients with mild to moderate COVID-19.

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Methods	Results	Limitations and Interpretation
COMET-ICE: Double-Blind RCT of Sotrovimab in Nonhospitalized Patients With Mild to Moderate COVID-19 in Brazil, Canada, Peru, Spain, and the United States[4]		
Key Inclusion Criteria: • Aged ≥18 years • ≥1 comorbidity or aged ≥55 years • Positive SARS-CoV-2 RT-PCR or antigen test result • Symptom onset ≤5 days before enrollment **Key Exclusion Criteria:** • Hospitalized or required supplemental oxygen • Severely immunocompromised **Interventions:** • SOT 500 mg IV (n = 528) • Placebo (n = 529) **Primary Endpoint:** • Hospitalization or death from any cause by Day 29	**Participant Characteristics:** • Median age 53 years; 20% aged ≥65 years; 54% women • 65% Hispanic/Latinx, 8% Black/African American • 63% with obesity; 22% with DM; 17% with moderate to severe asthma **Primary Outcome:** • Hospitalizations or all-cause deaths by Day 29: 6 (1%) in SOT arm vs. 30 (6%) in placebo arm, including 2 deaths (adjusted relative risk 0.21; 95% CI, 0.09–0.50; absolute difference -4.53%; 95% CI, -6.70% to -2.37%; $P < 0.001$)	**Key Limitation:** • Conducted before widespread circulation of the Omicron VOC **Interpretation:** • Compared to placebo, SOT reduced the incidence of all-cause hospitalizations and deaths among patients with mild to moderate COVID-19.

Key: BAM = bamlanivimab; bpm = beats per minute; BEB = bebtelovimab; CAS = casirivimab; DM = diabetes mellitus; ETE = etesevimab; IMD = imdevimab; IV = intravenous; mAb = monoclonal antibody; PEP = post-exposure prophylaxis; PHVL = persistently high viral load; RCT = randomized controlled trial; RT-PCR = reverse transcription polymerase chain reaction; SOT = sotrovimab; SpO_2 = oxygen saturation; VL = viral load; VOC = variant of concern

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COVID-19 Convalescent Plasma

Last Updated: April 29, 2022

Plasma from donors who have recovered from COVID-19 may contain antibodies to SARS-CoV-2 that could help suppress viral replication.[1] In August 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for COVID-19 convalescent plasma (CCP) for the treatment of hospitalized patients with COVID-19. The EUA was revised in February 2021 to limit the authorization to the use of high-titer CCP for the treatment of hospitalized patients with COVID-19 who are early in their disease course or who have impaired humoral immunity.[2] In December 2021, the EUA was revised again to authorize the use of CCP only in outpatients or inpatients with COVID-19 who have immunosuppressive disease or who are receiving immunosuppressive treatment. The testing criteria used to identify CCP products that contain high levels of anti-SARS-CoV-2 antibodies (i.e., high-titer products) was also revised.[2]

The use of CCP should be limited to high-titer products. Products that are not labeled "high titer" should not be used.

Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of CCP that was collected prior to the emergence of the Omicron (B.1.1.529) variant for the treatment of COVID-19 **(AIII)**.
- The Panel **recommends against** the use of CCP for the treatment of COVID-19 in hospitalized, immunocompetent patients **(AI)**.
- There is insufficient evidence for the Panel to recommend either for or against the use of high-titer CCP that was collected after the emergence of Omicron for the treatment of immunocompromised patients and nonhospitalized, immunocompetent patients with COVID-19.

Rationale

Regarding the Use of COVID-19 Convalescent Plasma Collected Prior to the Emergence of the Omicron Variant

The Omicron variant is the dominant SARS-CoV-2 variant currently circulating in the United States. Although in vitro data suggest that the CCP collected from vaccinated and unvaccinated individuals who have recovered from Omicron infection exhibits neutralizing activity against the Omicron variant,[3-6] it is not possible to extrapolate the potential clinical efficacy of CCP in the current clinical context. This is due in part to the following factors:

- The current supply of CCP products in the United States was not generated from donors who had recovered from Omicron infection.[7]
- Many CCP clinical trials were completed before the Omicron surge, and their results may not inform the current clinical context.
- The current approaches to testing CCP titers do not account for potential differences in the neutralizing activity of CCP products against currently circulating variants.

Furthermore, it is difficult to interpret the available data on the in vitro antiviral activity of CCP, since the published studies use a variety of assays to characterize the neutralizing activity of CCP, and the level of immunity to COVID-19 can vary across different donor populations.

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For Hospitalized, Immunocompetent Patients

Under the revised EUA, the use of CCP is no longer authorized for hospitalized patients who do not have immunosuppressive disease or who are not receiving immunosuppressive treatments.

Clinical data on the use of CCP for the treatment of COVID-19 in hospitalized, immunocompetent patients, including data from several randomized trials and the U.S. Expanded Access Program (EAP) for CCP, are summarized in Table 3b.

The initial EUA for CCP for the treatment of hospitalized patients with COVID-19 was issued on the basis of retrospective, indirect evaluations of efficacy generated from the CCP EAP, which allowed CCP to be used regardless of titer. Several retrospective analyses of the EAP data have indicated that patients who received high-titer CCP had a lower relative risk of death than patients who received low-titer CCP.[8,9] The Panel reviewed the EAP analyses and determined that the data were not sufficient to establish the efficacy or safety of CCP due to potential confounding factors, the lack of randomization, and the lack of an untreated control group.

Data from the initial randomized clinical trials that evaluated CCP, which were all underpowered, did not demonstrate the product's efficacy for the treatment of hospitalized patients with COVID-19.[10-17]

Subsequently, results from the 3 largest randomized clinical trials that evaluated CCP in hospitalized patients—RECOVERY,[18] CONCOR-1,[19] and REMAP-CAP[20]—found no evidence of benefit for high-titer CCP in hospitalized patients with COVID-19. All 3 were open-label trials that were stopped early due to futility.

Although these trials and the EAP did not exclude patients with impaired humoral immunity, most of the patients enrolled did not report a history of an immunocompromising condition or receipt of chronic immunosuppressive therapy. After reviewing the collective results from these studies, the Panel **recommends against** the use of CCP for the treatment of COVID-19 in hospitalized, immunocompetent patients **(AI)**.

For Nonhospitalized, Immunocompetent Patients

CCP is not authorized for the treatment of nonhospitalized patients with COVID-19 who do not have immunosuppressive disease or who are not receiving immunosuppressive treatment. Clinical data on the use of CCP for the treatment of nonhospitalized, immunocompetent patients are summarized in Table 3b. The data from well-designed clinical trials that evaluated the use of CCP for the treatment of nonhospitalized patients with COVID-19 are conflicting. All of the following trials were conducted prior to the emergence of Omicron.

Trials That Demonstrated Efficacy for COVID-19 Convalescent Plasma

- A moderately-sized, double-blind, placebo-controlled, randomized trial evaluated the use of high-titer CCP in older, nonhospitalized adults with <72 hours of mild COVID-19 symptoms (n = 160). The patients were aged ≥75 years or aged 65 to 74 years with ≥1 comorbidity. The trial reported a reduction in the proportion of patients who developed severe respiratory disease within 14 days in the CCP arm (16% in the CCP arm vs. 31% in the placebo arm; relative risk 0.52; 95% CI, 0.29–0.94; $P = 0.03$).[9]
- CSSC-004, a large (n = 1,181), double-blind, placebo-controlled trial that evaluated the use of high-titer CCP for the treatment of adults with ≤8 days of COVID-19 symptoms, demonstrated a reduction in the proportion of patients who experienced COVID-19-related hospitalization within 28 days in the CCP arm (2.9% in the CCP arm vs. 6.3% in the placebo arm; absolute risk reduction of 3.4 percentage points; 95% CI, 1.0–5.8; $P = 0.005$). Eighty-two percent of the patients were

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not vaccinated against COVID-19, and 53 of the 54 hospitalizations that were reported during the study occurred in unvaccinated patients. No hospitalizations occurred in either arm among fully vaccinated patients.[21]

Trials That Demonstrated No Benefit of COVID-19 Convalescent Plasma

- The SIREN-C3PO trial (n = 511) was a single-blind randomized trial that evaluated the use of high-titer CCP for the treatment of nonhospitalized patients with ≤7 days of mild or moderate COVID-19 symptoms and ≥1 risk factor for severe COVID-19. This study did not report a reduction in the proportion of patients who experienced disease progression in the CCP arm (30% in the CCP arm vs. 32% in the placebo arm; risk difference of 1.9 percentage points; 95% CrI, -6.0 to 9.8).[22]
- The CONV-ERT study (n = 376) was a double-blind, placebo-controlled randomized trial that evaluated the use of high-titer, methylene blue-treated CCP for the treatment of nonhospitalized patients aged ≥50 years with ≤7 days of mild or moderate COVID-19 symptoms. This study did not report a reduction in the proportion of patients who were hospitalized or died in the CCP arm (12% in the CCP arm vs. 11% in the placebo arm; relative risk 1.05; 95% CI, 0.78–1.41).[23]

Differences in patient populations, the placebo used (e.g., some studies used saline and some used non-SARS-CoV-2 plasma), and CCP manufacturing and testing methods may have contributed to the disparate outcomes of these clinical trials. Additional well-designed trials are necessary to establish evidence for a consistent benefit of using CCP in nonhospitalized patients during the current phase of the pandemic.

The emergence of SARS-CoV-2 variants further complicates the assessment of any potential benefit of CCP for this patient population. Most CCP products that are available in the United States are expected to have no or very little neutralizing activity against the currently circulating SARS-CoV-2 variants because they were collected from donors who had COVID-19 prior to the emergence of the Omicron variant. The Panel **recommends against** using CCP that was collected prior to the emergence of the Omicron variant for the treatment of COVID-19 **(AIII)**.

Currently, nonhospitalized patients with mild to moderate COVID-19 who are at high risk of progressing to severe disease are eligible to receive several antiviral therapies with proven efficacy. See Therapeutic Management of Nonhospitalized Adults With COVID-19 for the Panel's recommendations for this patient population.

Hospitalized or Nonhospitalized Patients Who Are Immunocompromised

This section pertains to people who are moderately or severely immunocompromised.[24] According to the Centers for Disease Control and Prevention, individuals who qualify as having moderately or severely immunocompromising conditions are those who:

- Are receiving active treatment for solid tumor and hematologic malignancies.
- Received a solid-organ transplant and are taking immunosuppressive therapy.
- Received chimeric antigen receptor T cell therapy or a hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy).
- Have a moderate or severe primary immunodeficiency (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome).
- Have advanced or untreated HIV infection (defined as people with HIV and CD4 T lymphocyte counts <200 cells/mm^3, a history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV).

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- Are receiving active treatment with high-dose corticosteroids (i.e., ≥20 mg prednisone or equivalent per day when administered for ≥2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumor-necrosis blockers, and other immunosuppressive or immunomodulatory biologic agents (e.g., B cell-depleting agents).

Under the EUA issued on December 27, 2021, CCP is authorized for the treatment of COVID-19 in outpatients or inpatients who have immunosuppressive disease or who are receiving immunosuppressive treatment.

Although there are no definitive data to support using CCP in patients who are immunocompromised, there is a physiologic rationale for the use of CCP in this patient population. People who are immunocompromised are more likely to require hospitalization for breakthrough SARS-CoV-2 infection despite COVID-19 vaccination, become severely ill from COVID-19, and experience prolonged SARS-CoV-2 infection and shedding.[25-27] Although some of this vulnerability may be attributed to impaired cellular immune responses, numerous studies indicate that people who are immunosuppressed are at risk of having reduced antibody responses to SARS-CoV-2 infection and/or vaccination.[28-30] Furthermore, the subgroup analyses from several clinical trials suggest that anti-SARS-CoV-2 antibody products are more likely to be effective in patients who are SARS-CoV-2 seronegative than in patients who are seropositive.[31,32] Therefore, patients who are immunocompromised could potentially benefit from receiving antibody-based therapies in circumstances where patients without an immunocompromising condition might not.

There are limited clinical data to inform the use of CCP to treat COVID-19 in patients who are immunocompromised. No randomized, adequately controlled trials evaluating CCP in immunocompromised patients have been published to date. A prespecified subgroup analysis of 126 critically ill REMAP-CAP participants with immunodeficiencies suggested that CCP might offer a potential benefit of improved survival and/or more organ support-free days in this subgroup (OR 1.51; 95% CI, 0.80–2.92); however, this finding was not statistically significant.[20] Data from case reports, case series, and a retrospective case-control study also suggest a potential benefit of CCP in patients with primary and secondary humoral immunodeficiencies, including patients with hematologic malignancy, common variable immune deficiency, or agammaglobulinemia, and those who have received a solid organ transplant.[33-46]

As noted above, the emergence of SARS-CoV-2 variants further complicates the assessment of any potential benefit of CCP for patients who are immunocompromised. Studies have shown that prior infection with the Beta (B.1.351) or Delta (B.1.617.2) variants affords little protection and has reduced neutralizing antibody responses against the Omicron variant, raising doubts that CCP collected prior to the emergence of Omicron will be effective.[47-50] Thus, the Panel **recommends against** the use of CCP collected prior to the emergence of the Omicron variant for the treatment of COVID-19 **(AIII)**.

There is insufficient evidence for the Panel to recommend either for or against the use of high-titer CCP that was collected after the emergence of Omicron for the treatment of COVID-19 in immunocompromised patients and nonhospitalized, immunocompetent patients. Adequately powered, well-designed, and well-conducted randomized clinical trials are needed to provide more specific, evidence-based guidance on the role of CCP in the treatment COVID-19 in patients who are immunocompromised.

Considerations in Pregnancy

The safety and efficacy of using CCP during pregnancy have not been evaluated in clinical trials, and published data on its use in pregnant individuals with COVID-19 are limited to case reports.[51]

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Pathogen-specific immunoglobulins (Ig) are used clinically during pregnancy to prevent infection from varicella zoster virus and rabies virus and have been used in clinical trials of congenital cytomegalovirus infection.[52,53] Pregnancy is not a reason to withhold CCP from a patient if it is otherwise indicated.

Considerations in Children

The safety and efficacy of CCP have not been systematically evaluated in pediatric patients. Published literature on its use in children is limited to case reports and case series. A few clinical trials that are evaluating the use of CCP in children are ongoing. The use of CCP may be considered on a case-by-case basis for hospitalized children who are immunocompromised and meet the EUA criteria for its use. CCP is not authorized by the FDA for use in immunocompetent patients.

As an alternative to CCP, several antiviral therapies are available for the treatment of children with COVID-19 who are at high risk of progressing to severe disease. The use of these products in children may be considered on a case-by-case basis. See Special Considerations in Children for more information.

Adverse Effects

The available data suggest that serious adverse reactions following the administration of CCP are infrequent and consistent with the risks associated with plasma infusions for other indications. These risks include transfusion-transmitted infections (e.g., HIV, hepatitis B, hepatitis C), allergic reactions, anaphylactic reactions, febrile nonhemolytic reactions, transfusion-related acute lung injury, transfusion-associated circulatory overload, and hemolytic reactions. Hypothermia, metabolic complications, and post-transfusion purpura have also been described.[2,18,54]

Additional risks of CCP transfusion include a theoretical risk of antibody-dependent enhancement of SARS-CoV-2 infection and a theoretical risk of long-term immunosuppression. In the CONCOR-1 trial, higher levels of full transmembrane spike IgG were associated with worse outcomes, suggesting that the use of CCP with nonfunctional anti-SARS-CoV-2 antibodies may be harmful.[19] A subgroup analysis in the REMAP-CAP trial showed potential harm in patients who received CCP transfusions more than 7 days after being hospitalized.[20]

When considering the use of CCP in patients with a history of severe allergic or anaphylactic transfusion reactions, consultation with a transfusion medicine specialist is advised.

Clinical Trials

Several randomized clinical trials that are evaluating the use of CCP for the treatment of COVID-19 are underway. Please see ClinicalTrials.gov for the latest information.

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Table 3b. COVID-19 Convalescent Plasma: Selected Clinical Data

Last Updated: April 29, 2022

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

Methods	Results	Limitations and Interpretation
REMAP-CAP: Multinational, Open-Label RCT of High-Titer CCP in Hospitalized Patients With Critical COVID-19[1]		

Key Inclusion Criterion:
• Admitted to ICU while receiving respiratory support (HFNC oxygen, NIV, MV, ECMO) and/or vasopressor or inotrope support
Key Exclusion Criteria:
• CCP contraindicated
• Death imminent
Interventions:
• High-titer CCP (550 mL +/- 150 mL) within 48 hours of randomization (n = 1,084)
• Usual care (n = 916)
Primary Endpoint:
• Organ support-free days by Day 21
Key Secondary Endpoints:
• In-hospital mortality
• Mortality by Day 28 and Day 90
• Respiratory support-free days
• ICU LOS
	Participant Characteristics:
	• Mean age 61 years; 68% men
	• 32% on MV
	• 29% were SARS-CoV-2 antibody negative at baseline
	• 94% received corticosteroids, 45% received RDV, 39% received IL-6 inhibitors
	Primary Outcome:
	• No difference between arms in median number of organ support-free days by Day 21: 0 days in CCP arm vs. 3 days in usual care arm (OR 0.97; 95% CrI, 0.82–1.14)
	Secondary Outcomes:
	• No difference between arms in:
	  • In-hospital mortality: 37% in CCP arm vs. 38% in usual care arm
	  • Mortality by Day 28 or Day 90
	  • Median number of respiratory support-free days: 0 days in CCP arm vs. 2 days in usual care arm
	  • Median ICU LOS: 21 days in CCP arm vs. 17 days in usual care arm
		Key Limitations:
		• Open-label study
		• Not all patients in CCP arm received CCP (86% received CCP as per protocol and 95% received some CCP).
		Interpretation:
		• There was no benefit of CCP in hospitalized patients with critical COVID-19.

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Methods	Results	Limitations and Interpretation
CONCOR-1: Multinational, Open-Label RCT of CCP for Hospitalized Patients With COVID-19 in Canada, the United States, and Brazil[2]		

Key Inclusion Criteria:
• Receipt of supplemental oxygen
• Within 12 days of respiratory symptom onset
Key Exclusion Criterion:
• Imminent or current intubation
Interventions:
• 1–2 units CCP (approximately 500 mL) from 1–2 donors (n = 625)
• SOC (n = 313)
Primary Endpoint:
• Intubation or death by Day 30
Key Secondary Endpoints:
• Time to intubation or death by Day 30
• Mortality by Day 30
• ICU LOS by Day 30
• Need for renal dialysis by Day 30
• Frequency of SAEs by Day 30
	Participant Characteristics:
	• Mean age 68 years; 59% men
	• 84% receiving systemic corticosteroids at enrollment
	Primary Outcome:
	• Intubation or death by Day 30: 32% in CCP arm vs. 28% in SOC arm (relative risk 1.16; 95% CI, 0.94–1.43, P = 0.18)
	Secondary Outcomes:
	• By Day 30, no difference between arms in:
	  • Time to intubation or death
	  • Mortality: 23% in CCP arm vs. 21% in SOC arm
	  • Mean ICU LOS: 4.3 days in CCP arm vs. 3.7 days in SOC arm
	  • Need for renal dialysis: 1.6% in CCP arm vs. 2.0% in SOC arm
	• Frequency of SAEs by Day 30: 33% in CCP arm vs. 26% in SOC arm
		Key Limitations:
		• Open-label study
		• Trial stopped at 78% of planned enrollment after meeting prespecified futility criteria for early termination.
		Interpretation:
		• There was no benefit of CCP in oxygen-dependent, hospitalized COVID-19 patients within 12 days of symptom onset.

RECOVERY: Open-Label RCT of High-Titer CCP in Hospitalized Patients in the United Kingdom[3]		

Key Inclusion Criterion:
• Clinically suspected or laboratory-confirmed SARS-CoV-2 infection
Key Exclusion Criterion:
• CCP contraindicated
Interventions:
• Approximately 275 mL per unit of CCP with IgG against SARS-CoV-2 spike protein, with sample to cutoff ratio ≥6.0. Administered as 2 units of high-titer CCP (first unit ASAP after randomization, second unit ≥12 hours later the next day) (n = 5,795)
• Usual care (n = 5,763)
	Participant Characteristics:
	• Mean age 64 years; 64% men
	• 5% on MV
	• 92% received corticosteroids
	Primary Outcomes:
	• No difference between arms in:
	  • Mortality: 24% in each arm
	  • Mortality in patients without detectable SARS-CoV-2 antibodies: 32% in CCP arm vs. 34% in usual care arm
	Secondary Outcomes:
	• No difference between arms in:
		Key Limitation:
		• Open-label study
		Interpretation:
		• There was no benefit of CCP in hospitalized patients with COVID-19.

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Methods	Results	Limitations and Interpretation
RECOVERY: Open-Label RCT of High-Titer CCP in Hospitalized Patients in the United Kingdom[3], continued		
Primary Endpoint: • All-cause mortality by Day 28 **Key Secondary Endpoints:** • Time to hospital discharge by Day 28 • Among patients not receiving MV, progression to MV or death by Day 28	• Proportion discharged by Day 28: 66% in both arms • Proportion who progressed to MV or death by Day 28: 29% in CCP arm vs. 29% in usual care arm	
CSSC-004: RCT of Early Treatment With High-Titer CCP in Outpatients With COVID-19 in the United States[4]		
Key Inclusion Criterion: • COVID-19 symptoms for <8 days **Key Exclusion Criteria:** • Prior or planned COVID-19–related hospitalization • Receipt of anti-SARS-CoV-2 mAbs **Interventions:** • Approximately 250 mL of CCP with SARS-CoV-2 spike-RBD IgG titer ≥1:320 (n = 592) • Non-SARS-CoV-2 plasma (n = 589) **Primary Endpoint:** • COVID-19–related hospitalization or all-cause death within 28 days	**Participant Characteristics:** • Median age 44 years; 7% aged ≥65 years; 57% women; 79% White • 8% with type 2 DM; 2% with CVD; 38% with BMI ≥30 • 82% were unvaccinated • Median time from symptom onset to transfusion was 6 days **Primary Outcomes:** • COVID-19–related hospitalization within 28 days: 2.9% in CCP arm vs. 6.3% in control arm (absolute risk reduction of 3.4 percentage points; 95% CI, 1.0–5.8; $P = 0.005$) • 53 of 54 hospitalizations occurred in unvaccinated individuals. None occurred in fully vaccinated individuals. • All-cause deaths within 28 days: 0 in CCP arm vs. 3 in control arm	**Key Limitation:** • Patients were at relatively low risk for disease progression. **Interpretation:** • This trial demonstrated a benefit of CCP in unvaccinated outpatients with <8 days of COVID-19 symptoms.

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Methods	Results	Limitations and Interpretation
CONV-ERT: RCT of High-Titer, Methylene Blue-Treated CCP as an Early Treatment for Outpatients With COVID-19 in Spain[5]		
Key Inclusion Criteria: • Aged ≥50 years • Mild or moderate COVID-19 symptoms for ≤7 days **Key Exclusion Criteria:** • Severe COVID-19 symptoms or requirement for hospitalization for any reason • Previous SARS-CoV-2 infection • Receipt of >1 COVID-19 vaccination **Interventions:** • 250–300 mL of high-titer, methylene blue-treated CCP (n = 188) • 0.9% saline (n = 188) **Primary Endpoints:** • Hospitalization within 28 days • Mean change in SARS-CoV-2 VL from baseline to Day 7 **Key Secondary Endpoints:** • Death by Day 60 • Time to complete symptom resolution	**Participant Characteristics:** • Mean age 56 years; 54% men • 75% with ≥1 risk factor for COVID-19 progression • 97% with mild COVID-19 • Median 4.4 days of symptoms prior to enrollment • Among the 369 patients for whom baseline serologic testing was available, 88% were negative for both IgG anti-SARS-CoV-2 spike and IgM anti-SARS-CoV-2 S1-RBD **Primary Outcomes:** • Hospitalization within 28 days: 12% in CCP arm vs. 11% in placebo arm (relative risk 1.05; 95% CrI, 0.78–1.41) • Mean change in SARS-CoV-2 VL: -2.41 $\log_{10}$ copies/mL in CCP arm vs. -2.32 $\log_{10}$ copies/mL in placebo arm **Key Secondary Outcomes:** • Death: 0 in CCP arm vs. 2 in placebo arm (relative risk 0.20; 95% CI 0.01–4.14) • No difference between arms in median time to symptom resolution: 12.0 days for both arms (HR 1.05; 95% CI, 0.85–1.30)	**Key Limitations:** • Trial was underpowered because it was terminated early due to rising vaccination rates among the eligible patient population. • Methylene blue, which was used for pathogen inactivation in donor plasma, could have potentially impaired Fc-region functionality of immunoglobulins and negatively impacted product efficacy and blinding. **Interpretation:** • This trial did not demonstrate a benefit of CCP in unvaccinated outpatients with <7 days of COVID-19 symptoms.
Double-Blind RCT of Early High-Titer CCP Therapy to Prevent Severe COVID-19 in Nonhospitalized Older Adults in Argentina[6]		
Key Inclusion Criteria: • Aged ≥75 years or aged 65–74 years with ≥1 coexisting condition • Mild COVID-19 symptoms for <72 hours **Key Exclusion Criterion:** • Severe respiratory disease **Interventions:** • 250 mL of CCP with IgG against SARS-CoV-2 spike protein >1:1,000 (n = 80) • Saline (n = 80)	**Participant Characteristics:** • Mean age 77 years; 38% men • Most with comorbidities **Primary Outcome:** • Severe respiratory disease by Day 15: 16% in CCP arm vs. 31% in placebo arm (relative risk 0.52; 95% CI, 0.29–0.94; $P = 0.03$)	**Key Limitations:** • Small sample size • Early termination because number of COVID-19 cases decreased **Interpretation:** • This trial demonstrated a benefit of CCP in older adult outpatients with <72 hours of mild COVID-19 symptoms.

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Methods	Results	Limitations and Interpretation
Double-Blind RCT of Early High-Titer CCP Therapy to Prevent Severe COVID-19 in Nonhospitalized Older Adults in Argentina[6]		
Primary Endpoint: • Severe respiratory disease, defined as respiratory rate ≥30 breaths/min and/or SpO_2 <93% on room air by Day 15		
SIREN-C3PO: Multicenter, Single-Blind RCT of High-Titer CCP in the United States[7]		
Key Inclusion Criteria: • ED patient with ≤7 days of symptoms • PCR-confirmed SARS-CoV-2 infection • Aged ≥50 years or aged ≥18 years with ≥1 risk factor for disease progression **Key Exclusion Criterion:** • Need for supplemental oxygen **Interventions:** • 250 mL high-titer CCP (median titer 1:641) (n = 257) • Saline (n = 254) **Primary Endpoint:** • Disease progression, defined as hospital admission, death, or seeking emergency or urgent care within 15 days of randomization **Key Secondary Endpoints:** • Severity of illness, as measured by an OS • All-cause mortality within 30 days • Hospital-free days over 30 days	**Participant Characteristics:** • Median age 54 years; 46% men • More patients with immunosuppression in CCP arm than in placebo arm (13% vs. 7%) • More patients with ≥3 risk factors in CCP arm than in placebo arm (55% vs. 48%) **Primary Outcomes:** • No difference between arms in proportion with disease progression: 30% in CCP arm vs. 32% in placebo arm (risk difference 1.9%; 95% CrI, -6.0% to 9.8%) • 25 patients (19 in CCP arm and 6 in placebo arm) required hospitalization during the index visit. In a post hoc analysis that excluded these patients, disease progression occurred in 24% in CCP arm vs. 30% in placebo arm (risk difference 5.8%; 95% CrI, -1.9% to 13.6%). **Secondary Outcomes:** • All-cause mortality within 30 days: 5 (1.9%) in CCP arm vs. 1 (0.4%) in placebo arm • No difference between arms in illness severity or mean number of hospital-free days	**Key Limitations:** • Imbalance of patients who required hospital admission during the index visit included in the primary analysis • Slightly more patients with multiple risk factors, including immunosuppression, in CCP arm **Interpretation:** • The use of high-titer CCP within 1 week of symptom onset did not prevent disease progression in outpatients with COVID-19 who were at high risk of severe disease.

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Methods	Results	Limitations and Interpretation
Retrospective Evaluation of CCP Antibody Levels and the Risk of Death From COVID-19 in the United States[8]		
Key Inclusion Criteria: • Severe or life-threatening COVID-19 • Patients for whom samples of transfused CCP were available for retrospective analysis of antibody titer **Interventions:** • High-titer CCP (n = 515), medium-titer CCP (n = 2,006), or low-titer CCP (n = 561), characterized retrospectively **Primary Endpoint:** • Mortality at 30 days after CCP transfusion	**Participant Characteristics:** • 31% aged ≥70 years; 61% men; 48% White, 37% Hispanic/Latinx • 61% in ICU; 33% on MV • 51% received corticosteroids, 31% received RDV **Primary Outcomes:** • Mortality at 30 days after transfusion: 22% in high-titer CCP arm vs. 27% in medium-titer CCP arm vs. 30% in low-titer CCP arm • High-titer CCP arm had a lower risk of death than low-titer CCP arm (relative risk 0.75; 95% CI, 0.61–0.93) • Mortality was lower among patients who were not receiving MV before CCP transfusion (relative risk 0.66; 95% CI, 0.48–0.91) • Among patients who were on MV before CCP transfusion, there was no difference in mortality between high-titer and low-titer arms (relative risk 1.02; 95% CI, 0.78–1.32)	**Key Limitation:** • Lack of untreated control arm **Interpretation:** • The study data are not sufficient to establish the efficacy or safety of COVID-19 CCP.

Key: ASAP = as soon as possible; BMI = body mass index; CCP = COVID-19 convalescent plasma; CVD = cardiovascular disease; DM = diabetes mellitus; ECMO = extracorporeal membrane oxygenation; ED = emergency department; Fc = fragment crystallizable; HFNC = high-flow nasal cannula; ICU = intensive care unit; Ig = immunoglobulin; IL = interleukin; LOS = length of stay; mAb = monoclonal antibody; MV = mechanical ventilation; NIV = noninvasive ventilation; OS = ordinal scale; the Panel = the COVID-19 Treatment Guidelines Panel; PCR = polymerase chain reaction; RBD = receptor binding domain; RCT = randomized controlled trial; RDV = remdesivir; SAE = serious adverse event; SOC = standard of care; SpO_2 = oxygen saturation; VL = viral load

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Immunoglobulins: SARS-CoV-2 Specific

Last Updated: July 17, 2020

Recommendation

- There is insufficient evidence 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.

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Table 3c. Characteristics of SARS-CoV-2 Antibody-Based Products

Last Updated: April 8, 2022

- The information in this table is based on data from investigational trials evaluating these products for the treatment or prevention of COVID-19. The table includes dose recommendations from the FDA EUAs for patients 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 or prevention 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 or prevention 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 the Panel's recommendations on using the drugs listed in this table, please refer to the Anti-SARS-CoV-2 Monoclonal Antibodies, Therapeutic Management of Nonhospitalized Adults With COVID-19, and Prevention of SARS-CoV-2 Infection sections of the Guidelines.

Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Bamlanivimab Plus Etesevimab (Anti-SARS-CoV-2 Monoclonal Antibodies) *Authorized for the treatment and PEP of COVID-19 under FDA EUA, but distribution has paused because the Omicron VOC has markedly reduced in vitro susceptibility to BAM plus ETE.*				
Dose Recommended in FDA EUA for Treatment and PEP of COVID-19 in Adults and Pediatric Patients Weighing ≥40 kg: • BAM 700 mg plus ETE 1,400 mg as a single IV infusion **Doses Recommended in FDA EUA for Treatment and PEP of COVID-19 in Neonates, Infants, Children, and Adolescents Weighing <40 kg:** • *1–12 kg:* BAM 12 mg/kg plus ETE 24 mg/kg as a single IV infusion	• Nausea • Dizziness • Pruritis • Hypersensitivity, including anaphylaxis and infusion-related reactions • These AEs were observed in multiple trials in which participants received either the authorized doses of BAM and ETE or higher doses of each drug.	• Only for administration in health care settings by qualified health care providers who have immediate access to emergency medical services and medications to treat severe infusion reactions. • Monitor during IV infusion and for ≥1 hour after infusion is completed.	• Drug-drug interactions are unlikely between BAM plus ETE and medications that are renally excreted or that are CYP substrates, inhibitors, or inducers.	**Availability:** • **Distribution of BAM plus ETE has paused** because the Omicron VOC has markedly reduced in vitro susceptibility to BAM plus ETE, and this regimen is not expected to provide clinical benefit. • HHS Public Health Emergency updates on the distribution of BAM plus ETE are available. • A list of clinical trials is available: Bamlanivimab Plus Etesevimab

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Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Bamlanivimab Plus Etesevimab (Anti-SARS-CoV-2 Monoclonal Antibodies), continued				
• *>12 kg to 20 kg:* BAM 175 mg plus ETE 350 mg as a single IV infusion • *>20 kg to <40 kg:* BAM 350 mg plus ETE 700 mg as a single IV infusion				
Bebtelovimab (Anti-SARS-CoV-2 Monoclonal Antibody) *Authorized for the treatment of COVID-19 under FDA EUA.*				
Dose Recommended in FDA EUA for Treatment of COVID-19 in Adults and Pediatric Patients Aged ≥12 Years and Weighing ≥40 kg: • BEB 175 mg as an IV injection over at least 30 seconds	• Nausea • Vomiting • Pruritis • Rash • Hypersensitivity, including anaphylaxis and infusion-related reactions	• Only for administration in health care settings by qualified health care providers who have immediate access to emergency medical services and medications to treat severe infusion reactions. • Monitor during IV injection and for ≥1 hour after injection is completed.	• Drug-drug interactions are unlikely between BEB and medications that are renally excreted or that are CYP substrates, inhibitors, or inducers.	**Availability:** • Under the FDA EUA, BEB is available for the treatment of high-risk outpatients with mild to moderate COVID-19.[1] See Anti-SARS-CoV-2 Monoclonal Antibodies for a list of high-risk conditions. • A list of clinical trials is available: Bebtelovimab
Casirivimab Plus Imdevimab (Anti-SARS-CoV-2 Monoclonal Antibodies) *Authorized for the treatment and PEP of COVID-19 under FDA EUA, but distribution has paused because the Omicron VOC has markedly reduced in vitro susceptibility to CAS plus IMD.*				
Dose Recommended in FDA EUA for Treatment and PEP of COVID-19 in Adults and Pediatric Patients Aged ≥12 Years and Weighing ≥40 kg: • CAS 600 mg plus IMD 600 mg as a single IV infusion over 1 hour • IV infusion is the preferred route of administration. However, when IV infusion is not feasible or would delay treatment, CAS 600 mg plus IMD 600 mg can be administered as 4 SUBQ injections (2.5 mL per injection) at 4 different sites. See	• Hypersensitivity, including anaphylaxis and infusion-related reactions • These AEs were observed in multiple trials in which participants received CAS 600 mg plus IMD 600 mg or higher doses of each drug. • Injection site reactions, including ecchymosis and erythema, in clinical trial participants who received CAS plus IMD as SUBQ injections	• Only for administration in health care settings by qualified health care providers who have immediate access to emergency medical services and medications to treat severe infusion reactions. • Monitor during IV infusion or SUBQ injections and for ≥1 hour after infusion or injections are completed.	• Drug-drug interactions are unlikely between CAS plus IMD and medications that are renally excreted or that are CYP substrates, inhibitors, or inducers.	**Availability:** • **Distribution of CAS plus IMD has paused** because the Omicron VOC has markedly reduced in vitro susceptibility to CAS plus IMD, and this regimen is not expected to provide clinical benefit. • HHS Public Health Emergency updates on the distribution of CAS plus IMD are available. • A list of clinical trials is available: Casirivimab Plus Imdevimab

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Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Casirivimab Plus Imdevimab (Anti-SARS-CoV-2 Monoclonal Antibodies), continued				
the FDA EUA for detailed information. **Dose Recommended in FDA EUA for PEP for Individuals With Ongoing Exposure to SARS-CoV-2:** • After initial dose, repeat dosing of CAS 300 mg plus IMD 300 mg by SUBQ injections or IV infusion every 4 weeks for duration of ongoing exposure.				
Sotrovimab (Anti-SARS-CoV-2 Monoclonal Antibody) *Authorized for the treatment of COVID-19 under FDA EUA, but distribution has paused in the United States because the Omicron BA.2 subvariant has markedly reduced in vitro susceptibility to SOT.*				
Dose Recommended in FDA EUA for Treatment of COVID-19 in Adults and Pediatric Patients Aged ≥12 Years and Weighing ≥40 kg: • SOT 500 mg as an IV infusion over 15 minutes for 50 mL bag or over 30 minutes for 100 mL bag	• Rash • Diarrhea • Hypersensitivity, including anaphylaxis and infusion-related reactions	• Only for administration in health care settings by qualified health care providers who have immediate access to emergency medical services and medications to treat severe infusion reactions. • Monitor during IV infusion and for ≥1 hour after infusion is completed.	• Drug-drug interactions are unlikely between SOT and medications that are renally excreted or that are CYP substrates, inhibitors, or inducers.	**Availability:** • **Distribution of SOT has paused** because the Omicron BA.2 subvariant has markedly reduced susceptibility to SOT, and SOT is not expected to provide clinical benefit. • HHS Public Health Emergency updates on the distribution of SOT are available. • A list of clinical trials is available: Sotrovimab
Tixagevimab Plus Cilgavimab (Evusheld) (Anti-SARS-CoV-2 Monoclonal Antibodies) *Authorized for PrEP of COVID-19 under FDA EUA.*				
Doses Recommended in FDA EUA for PrEP of COVID-19 in Adults and Pediatric Patients Aged ≥12 Years and Weighing ≥40 kg: • TIX 300 mg plus CIL 300 mg as 2 consecutive 3 mL IM injections	• Hypersensitivity, including anaphylaxis and injection-related reactions • In 1 clinical trial, cardiac events were reported in participants with cardiac	• Use with caution in individuals with thrombocytopenia or any coagulation disorder. • Monitor for ≥1 hour after injection.	• If a person has received a COVID-19 vaccine, TIX plus CIL should be administered ≥2 weeks after vaccination. • Drug-drug interactions are unlikely between	• Under the FDA EUA, TIX plus CIL for PrEP of COVID-19 is available for certain patients at high risk of infection. See Prevention of SARS-CoV-2 Infection for more information.[2]

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Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Tixagevimab Plus Cilgavimab (Evusheld) (Anti-SARS-CoV-2 Monoclonal Antibody), continued				
For patients who previously received a dose of TIX 150 mg plus CIL 150 mg, administer a second dose per the following criteria as soon as possible: • If the initial dose was ≤3 months ago, the second dose should be TIX 150 mg plus CIL 150 mg. • If the initial dose was >3 months ago, the second dose should be TIX 300 mg plus CIL 300 mg.	risk factors (0.6% in TIX plus CIL arm vs. 0.2% in placebo arm).		TIX plus CIL and medications that are renally excreted or that are CYP substrates, inhibitors, or inducers.	• A list of clinical trials is available: Tixagevimab Plus Cilgavimab
COVID-19 Convalescent Plasma *Authorized for the treatment of COVID-19 under FDA EUA.*				
Dose Recommended in FDA EUA for Treatment of COVID-19: • Per the EUA, consider starting clinical dosing with 1 high-titer COVID-19 CP unit (about 200 mL), with administration of additional CP units based on the prescribing provider's medical judgment and the patient's clinical response.	• TRALI • TACO • Allergic reactions • Anaphylactic reactions • Febrile nonhemolytic reactions • Hemolytic reactions • Hypothermia • Metabolic complications • Transfusion-transmitted infections[3] • Thrombotic events • Theoretical risk of antibody-mediated enhancement of infection and suppressed long-term immunity	• Before administering CP 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. • Monitor vital signs at baseline and during and after transfusion.	• Drug products **should not be added** to the IV infusion line for the blood product.	• The decision to use COVID-19 CP for the treatment of COVID-19 in patients aged <18 years should be based on an individualized assessment of risk and benefit.[4] • In patients with impaired cardiac function and heart failure, it may be necessary to reduce the CP volume or decrease the transfusion rate. **Availability:** • Under the FDA EUA, high-titer COVID-19 CP is available for hospitalized patients with COVID-19.[4] See Convalescent Plasma. • A list of clinical trials is available: COVID-19 Convalescent Plasma

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Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
SARS-CoV-2-Specific Immunoglobulin *Not approved by the FDA and not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*				
Dose in Clinical Trials for Treatment of COVID-19: • Dose varies by clinical trial.	• TRALI • TACO • Allergic reactions • Antibody-mediated enhancement of infection • RBC alloimmunization • Transfusion-transmitted infections[3]	• Monitor for transfusion-related reactions. • Monitor vital signs at baseline and during and after transfusion.	• Drug products **should not be added** to the IV infusion line for the blood product.	• A list of clinical trials is available: SARS-CoV-2 Immunoglobulin

Key: AE = adverse event; BAM = bamlanivimab; BEB = bebetelovimab; CAS = casirivimab; CIL = cilgavimab; CP = convalescent plasma; CYP = cytochrome P450; ETE = etesevimab; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; HHS = U.S. Department of Health and Human Services; IM = intramuscular; IMD = imdevimab; IV = intravenous; the Panel = the COVID-19 Treatment Guidelines Panel; PEP = post-exposure prophylaxis; PrEP = pre-exposure prophylaxis; RBC = red blood cell; SOT = sotrovimab; SUBQ = subcutaneous; TACO = transfusion-associated circulatory overload; TIX = tixagevimab; TRALI = transfusion-related acute lung injury; VOC = variant of concern

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

Last Updated: April 21, 2021

Mesenchymal Stem Cells

Mesenchymal stem cells are investigational products that have been studied extensively for broad clinical applications in regenerative 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 SARS-CoV-2.

Recommendation

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

Rationale for Recommendation

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

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

Rationale for Use in COVID-19

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

Clinical Data

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

Clinical Data for COVID-19

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

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

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

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

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

Clinical Data for Other Viral Infections

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

Clinical Trials

See 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 the potential for mesenchymal stem cells to multiply or change into inappropriate cell types, product contamination, growth of tumors, infections, thrombus formation, and administration site reactions.[11]

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Considerations in Pregnancy

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

Considerations in Children

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

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Immunomodulators Under Evaluation for the Treatment of COVID-19

Last Updated: December 16, 2021

Summary Recommendations
The hyperactive inflammatory response to SARS-CoV-2 infection plays a central role in the pathogenesis of COVID-19. See Therapeutic Management of Hospitalized Adults With COVID-19 for the COVID-19 Treatment Guidelines Panel's (the Panel) recommendations on the use of the following immunomodulators for hospitalized patients according to their disease severity: • Corticosteroids: dexamethasone • Interleukin-6 inhibitors: tocilizumab (or sarilumab) • Janus kinase (JAK) inhibitors: baricitinib (or tofacitinib) There is insufficient evidence for the Panel to recommend either for or against the use of the following immunomodulators for the treatment of COVID-19: • Anakinra • Fluvoxamine • Granulocyte-macrophage colony-stimulating factor inhibitors for hospitalized patients • Inhaled corticosteroids The Panel **recommends against** the use of the following immunomodulators for the treatment of COVID-19, except in a clinical trial: • **Baricitinib plus tocilizumab (AIII)** • **Canakinumab (BIIa)** • **Colchicine** for nonhospitalized patients **(BIIa)** • **Intravenous immunoglobulin (IVIG)** (non-SARS-CoV-2-specific) for the treatment of patients with acute COVID-19 **(AIII)**. This recommendation should not preclude the use of IVIG for multisystem inflammatory syndrome in children (MIS-C) or when it is otherwise indicated. • **Bruton's tyrosine kinase inhibitors** (e.g., **acalabrutinib, ibrutinib, zanubrutinib**) **(AIII)** • **JAK inhibitors** other than **baricitinib** and **tofacitinib** (e.g., **ruxolitinib**) **(AIII)** • **Siltuximab (BIII)** The Panel **recommends against** the use of the following immunomodulators for the treatment of COVID-19: • **Colchicine** for hospitalized patients **(AI)**
Rating of Recommendations: A = Strong; B = Moderate; C = Weak **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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Colchicine

Last Updated: May 31, 2022

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

Recommendations

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

Rationale: Nonhospitalized Patients

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

PRINCIPLE, an open-label, adaptive-platform, randomized trial that evaluated colchicine versus usual care, was stopped for futility when no significant difference was found between the colchicine and usual care recipients for the outcome of time to first self-reported recovery from COVID-19.[5]

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

Rationale: Hospitalized Patients

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

Clinical Data for COVID-19

COLCORONA Trial: Nonhospitalized Patients

The COLCORONA trial was a double-blind, placebo-controlled, randomized trial in outpatients who received a diagnosis of COVID-19 within 24 hours of enrollment.[4] Participants were aged ≥70 years or aged ≥40 years with at least 1 of the following criteria: body mass index ≥30, diabetes mellitus, uncontrolled hypertension, known respiratory disease, heart failure or coronary disease, fever ≥38.4°C

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within the past 48 hours, dyspnea at presentation, bicytopenia, pancytopenia, or the combination of high neutrophil count and low lymphocyte count. Participants were randomized 1:1 to receive placebo or colchicine 0.5 mg twice daily for 3 days, then once daily for 27 days. The primary endpoint was a composite of death or hospitalization by Day 30; secondary endpoints included components of the primary endpoint, as well as the need for mechanical ventilation by Day 30. Participants reported by telephone the occurrence of any study endpoints at 15 and 30 days after randomization; in some cases, clinical data were confirmed or obtained by medical chart reviews.

Results

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

Limitations

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

PRINCIPLE Trial: Nonhospitalized Patients

PRINCIPLE was a randomized, open-label, platform trial that evaluated colchicine in symptomatic, nonhospitalized patients with COVID-19.[5] Included participants had symptoms for ≤14 days and were aged ≥65 years or aged ≥18 years with comorbidities or shortness of breath. Participants were randomized to receive colchicine 0.5 mg daily for 14 days or usual care. The coprimary endpoints, which included time to first self-reported recovery or hospitalization or death due to COVID-19 by Day 28, were analyzed using a Bayesian model. Participants were followed through symptom diaries. Futility was defined as not reaching a clinically meaningful benefit (i.e., a hazard ratio ≥1.2, corresponding to about 1.5 days of faster recovery in the colchicine arm) for the endpoint of time to first self-reported recovery.

Results

- The study enrolled 4,997 participants: 212 participants were randomized to receive colchicine; 2,081 to receive usual care alone; and 2,704 to receive other treatments.
- The prespecified primary analysis included participants with a positive test for SARS-CoV-2 (156 participants in the colchicine arm; 1,145 in the usual care arm; and 1,454 in the other treatments arm).
- The trial stopped early because of futility; the median time to self-reported recovery was similar in the colchicine arm and the usual care arm (HR 0.92; 95% CrI, 0.72–1.16).

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- Analyses showed no significant differences between the colchicine and usual care arms for self-reported time to recovery and for hospitalizations or death due to COVID-19.
- There were no statistically significant differences between the colchicine and usual care arms for the secondary outcomes in both the primary analysis population and in the subgroups, including the subgroups based on symptom duration, baseline disease severity, age, and comorbidities.
- The occurrence of adverse events was similar in the colchicine and usual care arms.

Limitations

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

RECOVERY Trial: Hospitalized Patients

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

Results

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

Limitation

- The study had an open-label design.

COLCOVID Trial: Hospitalized Patients

COLCOVID was a multicenter, open-label, randomized trial in hospitalized adults with confirmed or suspected SARS-CoV-2.[7] Patients were assigned 1:1 to receive either colchicine (1.5 mg followed by 0.5 mg orally within 2 hours of initial dose, then twice daily for 14 days or until hospital discharge) plus usual care or usual care alone.

Results

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

Limitation

- The study had an open-label design.

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GRECCO-19 Trial: Hospitalized Patients

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

Results

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

Limitations

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

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

Adverse Effects, Monitoring, and Drug-Drug Interactions

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

Considerations in Pregnancy

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

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Considerations in Children

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

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Corticosteroids

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Multiple randomized trials indicate that systemic corticosteroid therapy improves clinical outcomes and reduces mortality in hospitalized patients with COVID-19 who require supplemental oxygen,[1,2] presumably by mitigating the COVID-19-induced systemic inflammatory response that can lead to lung injury and multisystem organ dysfunction. In contrast, in hospitalized patients with COVID-19 who do not require supplemental oxygen, the use of systemic corticosteroids has not shown any benefits and may cause harm.[3,4] The COVID-19 Treatment Guidelines Panel's (the Panel) recommendations for the use of corticosteroids in hospitalized patients with COVID-19 are based on results from these clinical trials (see Tables 4a and 4b for more information). There are no data to support the use of systemic corticosteroids in nonhospitalized patients with COVID-19.

Recommendations

For Nonhospitalized Adults With COVID-19

- See Therapeutic Management of Nonhospitalized Adults With COVID-19 for the Panel's recommendations on the use of dexamethasone or other systemic corticosteroids in certain nonhospitalized patients.
- There is insufficient evidence for the Panel to recommend either for or against the use of inhaled corticosteroids for the treatment of COVID-19 in these patients.
- Patients with COVID-19 who are receiving **dexamethasone** or **another corticosteroid** for an underlying condition should continue this therapy as directed by their health care provider **(AIII)**.

For Hospitalized Adults With COVID-19

- See Therapeutic Management of Hospitalized Adults With COVID-19 for the Panel's recommendations on the use of dexamethasone or other systemic corticosteroids in certain hospitalized patients.
- There is insufficient evidence for the Panel to recommend either for or against the use of inhaled corticosteroids for the treatment of COVID-19 in these patients.

Systemic Corticosteroids in Patients With COVID-19

Nonhospitalized Adults

There are no data to support the use of systemic corticosteroids in nonhospitalized patients with COVID-19. Therefore, the safety and efficacy of using systemic corticosteroids in this population have not been established. Generally, the use of systemic corticosteroids is associated with adverse events (e.g., hyperglycemia, neuropsychiatric symptoms, secondary infections), which may be difficult to detect and monitor in an outpatient setting. For more information, see General Management of Nonhospitalized Patients With Acute COVID-19.

Hospitalized Adults

The RECOVERY trial was a multicenter, open-label trial in the United Kingdom that randomly assigned 6,425 hospitalized patients to receive up to 10 days of dexamethasone 6 mg once daily plus standard care or standard care alone. Mortality at 28 days was lower among the patients who received dexamethasone than among those who received standard care alone.[3] This benefit of dexamethasone was observed in patients who were mechanically ventilated or who required supplemental oxygen at

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enrollment; in contrast, no benefit was seen in patients who did not require supplemental oxygen at enrollment.[3]

The CoDEX trial was a multicenter, open-label trial in Brazil that evaluated dexamethasone in patients who were mechanically ventilated due to acute respiratory distress syndrome (ARDS) induced by COVID-19. Although the trial was terminated early, the study results support the RECOVERY trial finding that systemic corticosteroids are beneficial in hospitalized patients with COVID-19. The trial randomly assigned 299 patients to receive either standard care plus intravenous (IV) dexamethasone 20 mg once daily for 5 days and then dexamethasone 10 mg IV once daily for 5 days or standard care alone. The mean number of days alive and free from mechanical ventilation over 28 days was greater in the dexamethasone arm than in the standard care alone arm. However, there were no differences between the arms in 28-day mortality, the mean number of intensive care unit-free days at 28 days, or the mean duration of mechanical ventilation at 28 days.[5]

An observational study evaluated the use of corticosteroids in 15,404 hospitalized patients with positive SARS-CoV-2 polymerase chain reaction results or antigen test results from the Department of Veteran Affairs' database.[4] Corticosteroids were administered to 60% of the patients within 48 hours of admission, and 95% of the patients who received corticosteroids received dexamethasone. A total of 9,450 patients did not receive supplemental oxygen during the study. Of these patients, 3,514 (37%) received dexamethasone, administered for a median duration of 5 days (IQR 3–8 days). Using average treatment effect estimates, patients who received dexamethasone without supplemental oxygen had an increased risk of death within 90 days (HR 1.76; 95% CI, 1.47–2.12). Patients who received dexamethasone either without supplemental oxygen or with low-flow nasal cannula oxygen had a 60% higher risk of death. Although this study was observational, the investigators employed several statistical techniques to minimize potential bias, including propensity scoring and weighted analyses. Additionally, several subgroup and sensitivity analyses in this study confirmed the overall results.

Dose of Dexamethasone

The COVID STEROID 2 trial is the largest study to date that has investigated the use of different doses of corticosteroids in people with COVID-19.[6] This multicenter trial randomized hospitalized patients to receive up to 10 days of once-daily dexamethasone 6 mg (n = 485) or dexamethasone 12 mg (n = 497). The median number of days alive without life support at 28 days after randomization was 20.5 days in the dexamethasone 6 mg arm (IQR 4.0–28.0 days) and 22.0 days in the dexamethasone 12 mg arm (IQR 6.0–28.0 days), yielding an adjusted mean difference of 1.3 days (95% CI, 0–2.6; $P = 0.07$). No differences were found in 28- or 90-day mortality between the arms. Approximately 12% of the patients in each arm received either an interleukin-6 inhibitor or a kinase inhibitor during the study. While these conventional analyses did not reach statistical significance, a preplanned Bayesian analysis found a higher probability of benefit and a lower probability of harm for the 12-mg dose than for the 6-mg dose.[7]

A smaller randomized controlled trial reported a shorter time to clinical improvement and a lower frequency of adverse events in patients with COVID-19 who received a lower dose of dexamethasone (8 mg IV once daily) compared to those who received higher doses (8 mg IV 2 or 3 times daily). A lower proportion of patients in the low-dose group died within 60 days compared to the intermediate- and high-dose groups (17% vs. 30% and 41%, respectively; $P = 0.06$). It is worth noting that this study included <200 participants.[8]

A third small, open-label, randomized trial (with <100 participants) found no difference in the median number of ventilator-free days at 28 days after randomization between patients who received higher doses of dexamethasone (16 mg IV daily for 5 days, followed by 8 mg daily for 5 days) and those who received lower doses (6 mg IV daily for 10 days).[9]

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The mixed results from these studies have led the Panel to continue to recommend 6 mg once daily as the preferred dose for dexamethasone. However, the Panel notes that both the traditional and Bayesian analyses conducted during the COVID STEROID 2 trial suggest that the 12-mg dose might confer a benefit in patients who require high levels of respiratory support. As a result, some clinicians might choose to use the higher dose of dexamethasone in these patients. It should be noted that there are currently no data evaluating the safety and efficacy of using lower or higher doses of corticosteroids in combination with other immunomodulators to treat COVID-19.

Combination Immunomodulator Therapy

Using systemic corticosteroids in combination with other agents, including tocilizumab (see Interleukin-6 Inhibitors)[10,11] or baricitinib (see Kinase Inhibitors),[12] has been shown to have a clinical benefit in subsets of hospitalized patients with COVID-19, especially those with early critical illness and/or those with signs of systemic inflammation. For the Panel's recommendations on when to use dexamethasone with another immunomodulator, see Therapeutic Management of Hospitalized Adults With COVID-19.

Please see Tables 4a and 4b for data from clinical trials that have evaluated the use of corticosteroids in patients with COVID-19.

Systemic Corticosteroids Other Than Dexamethasone

Systemic corticosteroids other than dexamethasone, including hydrocortisone[13,14] and methylprednisolone,[15,16] have been studied for the treatment of COVID-19 in several randomized trials. Some of these trials were stopped early due to under-enrollment following the release of the RECOVERY trial results. Consequently, the sample size of many these trials was insufficient to assess efficacy (i.e., there were too few events to definitively confirm or exclude an effect, although many point estimates suggested a beneficial effect). Therefore, the evidence supporting the use of hydrocortisone or methylprednisolone for the treatment of COVID-19 is not as strong as the evidence supporting the use of dexamethasone. Based on the available evidence, the Panel has concluded the following:

- If dexamethasone is not available, alternative glucocorticoids (e.g., prednisone, methylprednisolone, hydrocortisone) can be used.
- For these drugs, the total daily dose equivalencies to dexamethasone 6 mg (orally or IV)[17] 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 2 divided doses daily.
  - *Short-acting corticosteroid:* Hydrocortisone; half-life 8 to 12 hours, administer in 2 to 4 divided doses daily.
- Hydrocortisone is commonly used to manage septic shock in patients with COVID-19; see Hemodynamics for more information. Unlike other corticosteroids that have previously been studied in patients with ARDS, dexamethasone lacks mineralocorticoid activity and thus its effects on sodium balance and fluid volume are minimal.[18]

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Inhaled Corticosteroids in Patients With COVID-19

Inhaled corticosteroids have been identified as potential COVID-19 therapeutic agents because of their targeted anti-inflammatory effects on the lungs. In addition, certain inhaled corticosteroids have been shown to impair viral replication of SARS-CoV-2[19] and downregulate the expression of the receptors used for cell entry.[20,21] Two open-label randomized controlled trials and 2 double-blind, placebo-controlled trials provide additional insights regarding the role of inhaled corticosteroids in outpatients with COVID-19, as described below and in Table 4b.

Recommendation

- There is insufficient evidence for the Panel to recommend either for or against the use of inhaled corticosteroids for the treatment of COVID-19.

Rationale

Inhaled budesonide was studied in 2 open-label randomized controlled trials in outpatients with mild symptoms of COVID-19.[22,23] The small STOIC trial suggested that initiating inhaled budesonide in adult outpatients with mild COVID-19 may reduce the need for urgent care or emergency department assessment or hospitalization.[22] PRINCIPLE, a larger, open-label trial in nonhospitalized patients with COVID-19 who were at high risk of disease progression, found that using inhaled budesonide did not affect the rate of hospitalization or death but did reduce the time to self-reported recovery.[23] The findings from these trials should be interpreted with caution given the open-label design of the studies and other limitations.

Inhaled ciclesonide was studied in 2 double-blind, randomized, placebo-controlled trials in outpatients with mild COVID-19. The primary endpoint in 1 study was time to alleviation of COVID-19-related symptoms. In this study, the use of inhaled ciclesonide did not reduce the time to self-reported recovery, but the therapy did reduce the number of subsequent COVID-related emergency department visits or hospitalizations. The robustness of this conclusion is uncertain given the small number of events, which is likely due to the relatively small number of participants with comorbidities.[24] In the smaller CONTAIN study, the combined use of inhaled and intranasal ciclesonide did not improve the resolution of fever and/or respiratory symptoms by Day 7.[25]

The studies described above that evaluated the use of inhaled corticosteroid therapy in outpatients with mild COVID-19 have identified inconsistent effects of this therapy on subsequent hospitalization, and similar placebo-controlled trials have not demonstrated that this therapy improves the time to symptom resolution. The placebo-controlled studies did not enroll enough patients who were at high risk of disease progression; therefore, further studies in this population are needed. For additional information on these trials, see Table 4b.

Monitoring, Adverse Effects, and Drug-Drug Interactions

- Clinicians should closely monitor patients with COVID-19 who are receiving dexamethasone for certain adverse effects (e.g., hyperglycemia, secondary infections, psychiatric effects, avascular necrosis).
- Patients who are receiving inhaled corticosteroids may develop oral candidiasis.
- The use of systemic corticosteroids may increase the risk of opportunistic fungal infections (e.g., mucormycosis, aspergillosis) and reactivation of latent infections (e.g., hepatitis B virus infection, herpesvirus infections, strongyloidiasis, tuberculosis).[26-30]
- Cases of severe and disseminated strongyloidiasis have been reported in patients with COVID-19

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during treatment with tocilizumab and corticosteroids.[31,32] Many clinicians would initiate empiric antiparasitic treatment (e.g., with the antiparasitic drug ivermectin) with or without serologic testing in patients who currently reside or who have previously resided in areas where *Strongyloides* is endemic (i.e., tropical, subtropical, or warm temperate areas).[33]

- Using systemic corticosteroids with other immunosuppressants, such as tocilizumab or baricitinib, could theoretically increase the risk of secondary infections. However, clinical trials have reported no difference in the rates of secondary infections between patients who received corticosteroids in combination with another immunomodulatory agent and those who received corticosteroids alone.
- Dexamethasone is a moderate cytochrome P450 (CYP) 3A4 inducer. Therefore, it could reduce the concentration and potential efficacy of concomitant medications that are CYP3A4 substrates. Clinicians should carefully review a patient's concomitant medications to assess the potential for drug-drug interactions.
- Using a CYP3A4 inhibitor with inhaled budesonide may lead to increased systemic absorption of budesonide, which may result in systemic adverse effects from the corticosteroid.

Considerations in Pregnancy

A short course of betamethasone or dexamethasone, which are both known to cross the placenta, is routinely used to decrease neonatal complications of prematurity in women with threatened preterm delivery.[34,35]

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

Considerations in Children

The safety and effectiveness of using dexamethasone or other corticosteroids for COVID-19 treatment have not been sufficiently evaluated in pediatric patients. Caution is warranted when using data from clinical trials that enrolled adults to inform treatment recommendations for children, particularly younger children and those who are less severely ill. The Panel recommends using **dexamethasone** for children with COVID-19 who require high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation **(BIII)**. Corticosteroids are not routinely recommended for pediatric patients who require only low levels of oxygen support (i.e., administered via a nasal cannula only) but could be considered on a case-by-case basis. The use of dexamethasone for the treatment of severe COVID-19 in children who are profoundly immunocompromised has not been evaluated and may be harmful; therefore, such use should be considered only if the benefit is expected to outweigh the risks. The dexamethasone dosing regimen for pediatric patients is dexamethasone 0.15 mg/kg per dose (with a maximum dose of 6 mg) once daily for up to 10 days. There is insufficient evidence to recommend either for or against the use of inhaled corticosteroids in pediatric patients with COVID-19.

Methylprednisolone or **another corticosteroid** should be used in combination with IV immunoglobulin for the initial treatment of multisystem inflammatory syndrome in children (MIS-C) **(AIIb)**. The dosing regimen for initial therapy is methylprednisolone 1 to 2 mg/kg IV once daily or another glucocorticoid at an equivalent dose. See Therapeutic Management of Hospitalized Pediatric Patients With Multisystem Inflammatory Syndrome in Children (MIS-C) (With Discussion on Multisystem Inflammatory Syndrome in Adults [MIS-A]) for more information on the management of MIS-C.

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Clinical Trials

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

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Table 4a. Systemic Corticosteroids: Selected Clinical Data

Last Updated: May 31, 2022

The clinical trials described in this table do not represent all the trials that the Panel reviewed while developing the recommendations for systemic corticosteroids. The studies summarized below are those that have had the greatest impact on the Panel's recommendations. Unless stated otherwise, the clinical trials listed below only included participants aged ≥18 years.

Methods	Results	Limitations and Interpretation
RECOVERY: Open-Label RCT of Dexamethasone in Hospitalized Patients With COVID-19 in the United Kingdom[1]		

Key Inclusion Criterion:
• Hospitalized with suspected or laboratory-confirmed SARS-CoV-2 infection
Key Exclusion Criteria:
• Physician determination that risks of participation were too great based on patient's medical history
• An indication for corticosteroid therapy outside of the study
Interventions:
• DEX 6 mg IV or PO once daily plus SOC for up to 10 days or until discharge (n = 2,104)
• SOC alone (n = 4,321)
Primary Endpoint:
• All-cause mortality at 28 days
	Participant Characteristics:
	• Mean age 66 years; 64% men; 73% White
	• 56% had ≥1 comorbidity; 24% with DM
	• 89% had laboratory-confirmed SARS-CoV-2 infection
	• Median duration of DEX therapy: 7 days
	• At randomization:
	  • 16% received MV or ECMO
	  • 60% required supplemental oxygen but not MV
	  • 24% required no supplemental oxygen
	• Received RDV: <1% in both arms
	• Received tocilizumab or sarilumab: 2% in DEX arm vs. 3% in SOC arm
	Primary Outcome:
	• All-cause mortality at 28 days:
	  • All patients: 23% in DEX arm vs. 26% in SOC arm (age-adjusted rate ratio 0.83; 95% CI, 0.75–0.93; $P < 0.001$)
	  • Patients who required MV or ECMO at randomization: 29% in DEX arm vs. 41% in SOC arm (rate ratio 0.64; 95% CI, 0.51–0.81)
	  • Patients who required supplemental oxygen but not MV at randomization: 23% in DEX arm vs. 26% in SOC arm (rate ratio 0.82; 95% CI, 0.72–0.94)
	  • Patients who did not require supplemental oxygen at randomization: 18% in DEX arm vs. 14% in SOC arm (rate ratio 1.19, 95% CI, 0.92–1.55)
		Key Limitations:
		• Open-label study
		• Published data did not include results for key secondary endpoints (e.g., cause-specific mortality, need for renal replacement), AEs, and key subgroups (e.g., patients with comorbidities).
		• Patients who required supplemental oxygen (but not MV) had variable severity of illness. It is unclear whether all patients in this group benefited from DEX or whether benefit is restricted to those requiring higher levels of supplemental oxygen.
		• Patients aged >80 years were preferentially assigned to receive supplemental oxygen therapy (and not MV).
		• High mortality in this study may limit the generalizability of results to populations with a lower baseline mortality.
		Interpretation:
		• In hospitalized patients with severe COVID-19 who required supplemental oxygen, DEX reduced mortality at 28 days. The greatest benefit was seen in those receiving MV at randomization.
		• There was no survival benefit for DEX in patients who did not require supplemental oxygen at randomization.

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Methods	Results	Limitations and Interpretation
CoDEX: Open-Label RCT of Dexamethasone in Patients With Moderate or Severe ARDS and COVID-19 in Brazil[2]		

Key Inclusion Criteria:
• Confirmed or suspected SARS-CoV-2 infection
• Received MV within 48 hours of meeting criteria for moderate to severe ARDS (PaO_2/FiO_2 ≤200 mm Hg)
Key Exclusion Criteria:
• Received immunosuppressive drugs in past 21 days
• Death expected within 24 hours
Interventions:
• DEX 20 mg IV once daily for 5 days, then DEX 10 mg IV once daily for 5 days or until ICU discharge (n = 151)
• SOC alone (n = 148)
Primary Endpoint:
• Number of days alive and free from MV by Day 28
Key Secondary Endpoints:
• All-cause mortality by Day 28
• Number of ICU-free days by Day 28
• Duration of MV by Day 28
• Score on 6-point OS at Day 15
• SOFA score at Day 7
	Participant Characteristics:
	• Mean age 61 years; 63% men
	• Comorbidities:
	  • Obesity: 31% in DEX arm vs. 24% in SOC arm
	  • DM: 38% in DEX arm vs. 47% in SOC arm
	• Vasopressor use: 66% in DEX arm vs. 68% in SOC arm
	• Mean PaO_2/FiO_2: 131 mm Hg in DEX arm vs. 133 mm Hg in SOC arm
	• Median duration of DEX therapy: 10 days
	• No patients received RDV or tocilizumab
	• 35% in SOC arm received corticosteroids for indications such as bronchospasm or septic shock
	Primary Outcome:
	• Mean number of days alive and free from MV by Day 28: 7 in DEX arm vs. 4 in SOC arm ($P = 0.04$)
	Secondary Outcomes:
	• No differences between arms in all-cause mortality (56% vs. 62%), number of ICU-free days, duration of MV, or score on 6-point OS
	• Mean SOFA score at Day 7: 6.1 in DEX arm vs. 7.5 in SOC arm ($P = 0.004$)
	Other Outcome:
	• Post hoc analysis of probability of death or MV by Day 15: 68% in DEX arm vs. 80% in SOC arm (OR 0.46)
		Key Limitations:
		• Open-label study
		• Underpowered; enrollment stopped after release of data from the RECOVERY trial.
		• Patients discharged before 28 days were not followed for rehospitalization or mortality.
		• High mortality in this study may limit the generalizability of results to populations with a lower baseline mortality.
		• More than one-third of those randomized to receive SOC also received corticosteroids.
		Interpretation:
		• Compared with SOC alone, DEX increased the number of days alive and free of MV over 28 days in patients with COVID-19 and moderate to severe ARDS.

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Methods	Results	Limitations and Interpretation
Observational Cohort Study of Dexamethasone in Hospitalized Patients With COVID-19 Who Were Not on Intensive Respiratory Support in the United States[3]		

Key Inclusion Criterion:
• Within 14 days of a positive test result for SARS-CoV-2 infection
Key Exclusion Criteria:
• Recent receipt of corticosteroids
• Receipt of IRS (defined as HFNC oxygen, NIV, or MV) within 48 hours
• Hospital LOS of <48 hours
Interventions:
• Corticosteroids (95% of patients received DEX) administered within 48 hours of admission (n = 7,507)
• No corticosteroids administered (n = 7,433)
Primary Endpoint:
• All-cause mortality at 90 days
	Participant Characteristics:
	• Mean age 71 years; 95% men; 27% Black, 55% White
	• 77% did not receive IRS within 48 hours
	• 83% admitted within 1 day after positive SARS-CoV-2 test result
	• Median duration of DEX for patients who did not receive IRS: 5 days for patients who were not on supplemental oxygen at baseline vs. 6 days for patients on low-flow nasal cannula oxygen
	• Received RDV: 43% of those who received DEX vs. 13% of those who did not
	• Received anticoagulants: 46% of those who received DEX vs. 10% of those who did not
	Primary Outcome:
	• Risk of all-cause mortality at 90 days was higher in those who received DEX:
	  • For combination of those not on supplemental oxygen and those on low-flow nasal cannula oxygen: HR 1.59; 95% CI, 1.39–1.81
	  • For those not on supplemental oxygen: HR 1.76; 95% CI, 1.47–2.12
	  • For those on low-flow nasal cannula oxygen: HR 1.08; 95% CI, 0.86–1.36
		Key Limitations:
		• Retrospective observational study
		• Because nearly all patients on MV or HFNC oxygen received DEX, analysis was restricted to patients who did not receive IRS (i.e., those who received no supplemental oxygen or only low-flow nasal cannula oxygen).
		• Differences between the arms in other therapies received
		Interpretation:
		• In hospitalized patients with COVID-19, the use of DEX was not associated with a mortality benefit among those who received low-flow nasal cannula oxygen during the first 48 hours after admission, but it was associated with increased mortality among those who received no supplemental oxygen during the first 48 hours after admission.

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Methods	Results	Limitations and Interpretation
COVID STEROID 2: Blinded RCT of Dexamethasone 12 mg Versus 6 mg in Hospitalized Adults With COVID-19 and Severe Hypoxemia in Denmark, India, Sweden, and Switzerland[4,5]		

Key Inclusion Criteria:
• Confirmed SARS-CoV-2 infection
• Requiring oxygen ≥10 L/min, NIV, CPAP, or MV
Key Exclusion Criteria:
• Treated with DEX >6 mg (or equivalent)
• Treated with a corticosteroid within past 5 days
• Invasive fungal infection or active TB
Interventions:
• DEX 12 mg IV once daily for up to 10 days (n = 497)
• DEX 6 mg IV once daily for up to 10 days (n = 485)
Primary Endpoint:
• Number of days alive without life support (MV, circulatory support, or kidney replacement therapy) at 28 days
Key Secondary Endpoints:
• Number of days alive without life support at 90 days
• Number of days alive and out of hospital at 90 days
• Mortality at 90 days
• Mortality at 28 days
• SAEs at 28 days
	Participant Characteristics:
	• Median age 65 years; 31% women
	• DM: 27% in 12 mg arm vs. 34% in 6 mg arm
	• Median time from symptom onset to hospitalization: 7 days in both arms
	• Received ICU care: 78% in 12 mg arm vs. 81% in 6 mg arm
	• Oxygen requirements:
	  • 54% on oxygen via nasal cannula or face mask (median flow rate 23 L/min)
	  • 25% on NIV
	  • 21% on MV
	• 63% received RDV; 12% received IL-6 inhibitors or JAK inhibitors
	• Median duration of DEX treatment: 7 days in both arms
	Primary Outcome:
	• Median number of days alive without life support: 22.0 in 12 mg arm vs. 20.5 in 6 mg arm (adjusted mean difference 1.3 days; 95% CI, 0.0–2.6; $P = 0.07$)
	  • 63.9% Bayesian probability of clinically important benefit and 0.3% Bayesian probability of clinically important harm for DEX 12 mg
	Secondary Outcomes:
	• At 90 days:
	  • Median number of days alive without life support: 84 in 12 mg arm vs. 80 in 6 mg arm ($P = 0.15$)
	  • Median number of days alive and out of hospital: 62 in 12 mg arm vs. 48 in 6 mg arm ($P = 0.09$)
	  • Mortality: 32% in 12 mg arm vs. 38% in 6 mg arm (adjusted relative risk 0.87; 99% CI, 0.70–1.07; $P = 0.09$)
		Key Limitation:
		• The randomized intervention period was <10 days in some patients because the trial allowed up to 4 days of DEX before enrollment.
		Interpretation:
		• Among patients with COVID-19 and severe hypoxemia, the use of DEX 12 mg once daily did not result in more days alive without life support at 28 days than DEX 6 mg once daily.

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Methods	Results	Limitations and Interpretation
COVID STEROID 2: Blinded RCT of Dexamethasone 12 mg Versus 6 mg in Hospitalized Adults With COVID-19 and Severe Hypoxemia in Denmark, India, Sweden, and Switzerland[4,5], continued		
	• At 28 days: • Mortality: 27% in 12 mg arm vs. 32% in 6 mg arm (adjusted relative risk 0.86; 99% CI, 0.68–1.08; $P = 0.10$) • SAEs, including septic shock and invasive fungal infections: 11% in 12 mg arm vs. 13% in 6 mg arm (adjusted relative risk 0.83; 99% CI, 0.54–1.29; $P = 0.27$)	
CAPE COVID: Double-Blind RCT of Hydrocortisone Among Critically Ill Patients With COVID-19 in France[6]		
Key Inclusion Criteria: • Laboratory-confirmed SARS-CoV-2 infection or radiographically suspected COVID-19 with ≥1 of the following: • MV with PEEP ≥5 cm H_2O • PaO_2/FiO_2 <300 mm Hg and FiO_2 ≥50% on HFNC • PaO_2/FiO_2 <300 mm Hg on reservoir mask oxygen • Pulmonary severity index >130 **Key Exclusion Criteria:** • Septic shock • Do-not-intubate orders **Interventions:** • Continuous IV infusion of hydrocortisone 200 mg per day for 7 days, then 100 mg per day for 4 days, then 50 mg per day for 3 days. If patient improved by Day 4, then IV infusion of hydrocortisone 200 mg per day for 4 days, then 100 mg per day for 2 days, then 50 mg per day for 2 days (n = 76) • Placebo (n = 73)	**Participant Characteristics:** • Mean age 62 years; 70% men; median BMI 28 • 96% had laboratory-confirmed SARS-CoV-2 infection • Median symptom duration: 9–10 days • Required MV at baseline: 81% • Received vasopressors: 24% in hydrocortisone arm vs. 18% in placebo arm • Received RDV or tocilizumab: <5% • Median duration of treatment with study drug: 11 days in hydrocortisone arm vs. 13 days in placebo arm ($P = 0.25$) **Primary Outcome:** • Treatment failure by Day 21: 42% in hydrocortisone arm vs. 51% in placebo arm ($P = 0.29$) **Secondary Outcomes:** • No difference between arms in need for intubation or prone positioning (too few patients received ECMO or inhaled nitric oxide for comparisons) • Among patients who did not require MV at baseline, 50% in hydrocortisone arm vs. 75% in placebo arm required subsequent MV • No difference between arms in proportion of patients with nosocomial infection by Day 28	**Key Limitations:** • Underpowered; enrollment stopped after release of data from the RECOVERY trial, resulting in limited power to detect differences between arms. • Limited information about comorbidities **Interpretation:** • The use of hydrocortisone did not reduce the proportion of patients with COVID-19 and acute respiratory failure who experienced treatment failure by Day 21.

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Methods	Results	Limitations and Interpretation
CAPE COVID: Double-Blind RCT of Hydrocortisone Among Critically Ill Patients With COVID-19 in France[6], continued		

Primary Endpoint:
• Treatment failure (death or dependency on MV or high-flow oxygen) by Day 21
Key Secondary Endpoints:
• Need for MV, prone positioning, ECMO, or inhaled nitric oxide
• Nosocomial infection by Day 28
• Clinical status on Day 21, as measured by a 5-item scale:
  • Death
  • In ICU and on MV
  • Required high-flow oxygen therapy
  • Required low-flow oxygen therapy
  • Discharged from ICU
	• No difference between arms in clinical status on Day 21, but 15% died in hydrocortisone arm vs. 27% in placebo arm (P = 0.06)
	• Discharged from ICU by Day 21: 57% in hydrocortisone arm vs. 44% in placebo arm; 23% in both arms still required MV	

REMAP-CAP: Randomized, Open-Label, Adaptive Trial of Hydrocortisone in Patients With Severe COVID-19[7]		

Key Inclusion Criteria:
• Presumed or laboratory-confirmed SARS-CoV-2 infection
• ICU admission for respiratory or cardiovascular support
Key Exclusion Criteria:
• Presumed imminent death
• Systemic corticosteroid use
• >36 hours since ICU admission
Interventions:
• Hydrocortisone 50 mg IV every 6 hours for 7 days (n = 137)
• Shock-dependent hydrocortisone 50 mg IV every 6 hours for duration of shock for up to 28 days (n = 146)
• No hydrocortisone (n = 101)
	Participant Characteristics:
	• Mean age 60 years; 71% men; 53% White
	• Mean BMI 29.7–30.9
	• 50% to 64% required MV
	Primary Outcome:
	• No difference between arms in median number of organ support-free days at Day 21 (0 in each arm)
	• Median adjusted ORs for primary outcome for hydrocortisone arms compared to no hydrocortisone arm:
	  • OR 1.43 (95% CrI, 0.91–2.27) with 93% Bayesian probability of superiority for fixed-dose hydrocortisone arm
	  • OR 1.22 (95% CrI, 0.76–1.94) with 80% Bayesian probability of superiority for shock-dependent hydrocortisone arm
	Key Secondary Outcome:
	• No difference between arms in in-hospital mortality (30% in
		Key Limitations:
		• Open-label study
		• Enrollment stopped after release of data from the RECOVERY trial.
		Interpretation:
		• The use of hydrocortisone did not increase the median number of support-free days in either the fixed-dose or the shock-dependent hydrocortisone arms, although early termination limited the study's power to detect differences between the study arms.

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Methods	Results	Limitations and Interpretation
REMAP-CAP: Randomized, Open-Label, Adaptive Trial of Hydrocortisone in Patients With Severe COVID-19[7], continued		
Primary Endpoint: • Number of days free from respiratory and cardiovascular support by Day 21 **Key Secondary Endpoint:** • In-hospital mortality	fixed-dose hydrocortisone arm vs. 26% in shock-dependent hydrocortisone arm vs. 33% in no hydrocortisone arm)	
Single-Blind RCT of Methylprednisolone in Hospitalized Patients With COVID-19 Pneumonia in China[8]		

Key Inclusion Criteria:
• Laboratory-confirmed SARS-CoV-2 infection
• Pneumonia confirmed by chest CT scan
• Hospitalized on general ward for <72 hours
Key Exclusion Criteria:
• Severe immunosuppression
• Corticosteroid use for other diseases
Interventions:
• Methylprednisolone 1 mg/kg per day IV for 7 days (n = 43)
• Saline (n = 43)
Primary Endpoint:
• Clinical deterioration at 14 days
Key Secondary Endpoints:
• Clinical cure at 14 days
• Time to clinical cure
• ICU admission
• In-hospital mortality
• Number of days hospitalized
	Participant Characteristics:
	• Mean age 56 years; 48% men
	• Median time from symptom onset to randomization: 8 days
	• At randomization, 71% were receiving oxygen via nasal cannula
	Primary Outcome:
	• Clinical deterioration at 14 days: 4.8% in both arms (OR 1.0; 95% CI, 0.134–7.442; $P = 1.00$)
	Secondary Outcomes:
	• No differences (all $P > 0.05$) between methylprednisolone arm and placebo arm for:
	  • Clinical cure at 14 days: 51% vs. 58%
	  • Median number of days to clinical cure: 14 vs. 12
	  • ICU admission: 4.8% in both arms
	  • In-hospital mortality: 0% vs. 2.3%
	  • Median number of days hospitalized: 17 vs. 13
		Key Limitations:
		• Small sample size
		• Terminated early because of decreasing incidence of COVID-19 pneumonia at study sites
		Interpretation:
		• The incidence of clinical deterioration did not differ between the methylprednisolone and placebo arms.

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Methods	Results	Limitations and Interpretation
Single-Blind RCT of 3 Doses of Dexamethasone in Hospitalized Patients With Moderate to Severe COVID-19 in Iran[9]		
Key Inclusion Criteria: • PCR-confirmed SARS-CoV-2 infection or CT scan showing lung involvement • Moderate or severe COVID-19 • Requirement for supplemental oxygen **Key Exclusion Criteria:** • Uncontrolled DM • Active fungal or parasitic infection • On MV or receiving vasopressor therapy **Interventions:** • Low dose: DEX 8 mg IV once daily for up to 10 days (n = 47) • Intermediate dose: DEX 8 mg IV twice daily for up to 10 days (n = 40) • High dose: DEX 8 mg IV 3 times a day for up to 10 days (n = 46) **Primary Endpoint:** • Time to clinical response, as measured by OS **Key Secondary Endpoints:** • Mortality at 60 days • Occurrence of AEs	**Participant Characteristics:** • Mean age: 59 years in low-dose arm vs. 59 years in intermediate-dose arm vs. 56 years in high-dose arm • 50% men • 23% with DM • 75% received RDV **Primary Outcome:** • Mean number of days to clinical response: 4.3 in low-dose arm vs. 5.3 in intermediate-dose arm vs. 6.1 in high-dose arm ($P = 0.025$) **Secondary Outcomes:** • Mortality at 60 days: 17% in low-dose arm vs. 30% in intermediate-dose arm vs. 41% in high-dose arm ($P = 0.06$) • AEs (leukocytosis, hyperglycemia, and secondary infections) occurred more frequently in intermediate-dose and high-dose arms than in low-dose arm; however, this result was not statistically significant.	**Key Limitation:** • Small sample size **Interpretation:** • The time to clinical response was significantly shorter in the low-dose DEX arm than in the intermediate- or high-dose arms. Patients in the low-dose arm had a higher probability of survival than those in the high-dose arm.

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Methods	Results	Limitations and Interpretation
Open-Label Randomized Trial of High-Dose Versus Low-Dose Dexamethasone in Patients With COVID-19-Related ARDS in Argentina[10]		

Key Inclusion Criteria:
• Laboratory-confirmed SAR-CoV-2 infection
• ARDS
• On MV for <72 hours
Key Exclusion Criteria:
• Presumed imminent death
• Immunosuppression
• Treatment with glucocorticoids
Interventions:
• High dose: DEX 16 mg IV once daily for 5 days, followed by DEX 8 mg IV once daily for 5 days (n = 49)
• Low dose: DEX 6 mg once daily IV for 10 days (n = 49)
Primary Endpoints:
• Number of ventilator-free days by Day 28
• Time to discontinuation of MV
Key Secondary Endpoint:
• All-cause mortality by Day 28 and Day 90
	Participant Characteristics:
	• Mean age: 60 years in high-dose arm vs. 63 years in low-dose arm
	• 30% women
	Primary Outcomes:
	• Median number of ventilator-free days by Day 28: 0 for both arms ($P = 0.23$)
	• No difference between arms in mean duration of MV by Day 28 (19 ± 18 days in high-dose arm vs. 25 ± 22 days in low-dose arm; $P = 0.078$). Cumulative hazard of successful discontinuation from MV was greater in high-dose arm than low-dose arm (adjusted subdistribution HR 1.84; 95% CI, 1.31–2.5; $P < 0.001$).
	Secondary Outcome:
	• All-cause mortality:
	  • By Day 28: 41% in high-dose arm vs. 39% in low-dose arm ($P > 0.999$)
	  • By Day 90: 47% in both arms ($P > 0.999$)
		Key Limitations:
		• Small, open-label study
		• Trial was prematurely terminated due to low enrollment rate.
		Interpretation:
		• The use of a higher dose of DEX did not increase the median number of ventilator-free days in patients with ARDS due to COVID-19. However, the higher dose shortened the time to discontinuation of MV.

Key: AE = adverse event; ARDS = acute respiratory distress syndrome; BMI = body mass index; CPAP = continuous positive airway pressure; CT = computed tomography; DEX = dexamethasone; DM = diabetes mellitus; ECMO = extracorporeal membrane oxygenation; HFNC = high-flow nasal cannula; ICU = intensive care unit; IL = interleukin; IRS = intensive respiratory support; IV = intravenous; JAK = Janus kinase; LOS = length of stay; MV = mechanical ventilation; NIV = noninvasive ventilation; OS = ordinal scale; the Panel = the COVID-19 Treatment Guidelines Panel; PaO_2/FiO_2 = ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; PCR = polymerase chain reaction; PEEP = positive end-expiratory pressure; PO = orally; RCT = randomized controlled trial; RDV = remdesivir; SAE = serious adverse event; SOC = standard of care; SOFA = sequential organ failure assessment; TB = tuberculosis

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Table 4b. Inhaled Corticosteroids: Selected Clinical Data

Last Updated: December 16, 2021

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

Methods	Results	Limitations and Interpretation
PRINCIPLE: Open-Label RCT of Inhaled Budesonide in Nonhospitalized Patients With COVID-19[1]		
Key Inclusion Criteria: • Aged ≥65 years or aged ≥50 years with comorbidities • PCR-confirmed or suspected COVID-19 • ≤14 days of symptoms **Key Exclusion Criteria:** • Already taking inhaled or systemic corticosteroids • Unable to use an inhaler • Contraindication to inhaled budesonide **Interventions:** • Usual care plus budesonide 800 mcg inhaled twice daily for 14 days (n = 1,069) • Usual care (n = 787) **Primary Endpoints:** • COVID-19-related hospitalization or death up to 28 days from randomization • Time to reported recovery up to 28 days from randomization	**Participant Characteristics:** • Mean age 64.2 years; 52% women; 92% White • 81% with comorbidities • Median time from symptom onset to randomization: 6 days **Primary Outcomes:** • Percentage of patients who were hospitalized or died due to COVID-19 within 28 days: 6.8% in budesonide arm vs. 8.8% in usual care arm (OR 0.75; 95% CrI, 0.55–1.03). • Median time to reported recovery: 11.8 days in budesonide arm vs. 14.7 days in usual care arm (HR 1.21; 95% CrI, 1.08–1.36).	**Key Limitations:** • Open-label trial • Primary endpoint of time to reported recovery based on participant self-report **Interpretation:** • Inhaled budesonide reduced time to reported recovery but not COVID-19-related hospitalization or death. • The clinical significance of self-reported time to recovery in an open-label study is unclear.
STOIC: Open-Label, Phase 2 RCT of Inhaled Budesonide in Nonhospitalized Adults With Early COVID-19[2]		
Key Inclusion Criteria: • Aged ≥18 years • ≤7 days of symptoms **Key Exclusion Criteria:** • Use of inhaled or systemic glucocorticoids in past 7 days • Known allergy or contraindication to budesonide **Interventions:** • Usual care plus budesonide 800 mcg inhaled twice daily until symptom resolution (n = 73)	**Participant Characteristics:** • Mean age 45 years; 58% women • 9% with CVD, 5% with DM • 95% with positive SARS-CoV-2 RT-PCR result • Median time from symptom onset to randomization: 3 days	**Key Limitations:** • Small, open-label trial • Early termination after statistical analysis determined that additional participants would not alter study outcome

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Methods	Results	Limitations and Interpretation
STOIC: Open-Label, Phase 2 RCT of Inhaled Budesonide in Nonhospitalized Adults with Early COVID-19[2], continued		
• Usual care (n = 73) **Primary Endpoint:** • COVID-19-related urgent care visit, including ED visit or hospitalization	**Primary Outcomes:** • Median duration of budesonide use: 7 days. • Percentage of patients with COVID-19-related urgent care visit or hospitalization: 1% in budesonide arm vs.14% in usual care arm (relative risk reduction 91%).	**Interpretation:** • In adult outpatients with mild COVID-19, inhaled budesonide may reduce the need for urgent care or ED assessment and/or hospitalization.
Phase 3, Double-Blind RCT of Inhaled Ciclesonide in Nonhospitalized Patients With COVID-19[3]		

Key Inclusion Criteria:
• Aged ≥12 years
• Positive SARS-CoV-2 molecular or antigen diagnostic test result in previous 72 hours
• ≥1 symptom of fever, cough, or dyspnea
Key Exclusion Criteria:
• Taken inhaled or intranasal corticosteroid within 14 days of enrollment or systemic corticosteroid within 90 days of enrollment
• Unable to use an inhaler
Interventions:
• Ciclesonide MDI 160 µg/actuation, 2 actuations twice a day for 30 days (n = 197)
• Placebo MDI twice a day for 30 days (n = 203)
Primary Endpoint:
• Time to alleviation of all COVID-19-related symptoms by Day 30
Key Secondary Endpoints:
• Alleviation of COVID-19-related symptoms by Day 30
• ED visit or hospital admission for COVID-19 by Day 30
• Hospital admission or death by Day 30
	Participant Characteristics:
	• Mean age 43.3 years; 55.3% women; 86.3% White
	• Mean BMI 29.4
	• 22.3% with HTN, 7.5% with type 2 DM
	• Higher rates of DM and asthma in ciclesonide arm
	Primary Outcome:
	• Median time to alleviation of all COVID-19-related symptoms: 19.0 days in ciclesonide arm vs. 19.0 days in placebo arm (HR 1.08; 95% CI, 0.84–1.38).
	Secondary Outcomes:
	• By Day 30, percentage of patients in whom the following outcomes occurred:
	  • Alleviation of COVID-19-related symptoms: 70.6% in ciclesonide arm vs. 63.5% in placebo arm.
	  • Subsequent ED visit or hospital admission for COVID-19: 1.0% in ciclesonide arm vs. 5.4% in placebo arm (OR 0.18; 95% CI, 0.04–0.85).
	  • Hospital admission or death: 1.5% in ciclesonide arm vs. 3.4% in placebo arm (OR 0.45; 95% CI, 0.11–1.84).
	• No deaths by Day 30 in either arm.
		Key Limitations:
		• ED or hospitalization outcome based on small number of events
		• Primary endpoint of time to alleviation of all symptoms based on participant self-report
		Interpretation:
		• Inhaled ciclesonide did not reduce time to reported recovery.
		• The robustness of the conclusion that inhaled ciclesonide reduced COVID-19-related ED visits or hospitalization is uncertain; there were only a small number of events, which is most likely due to the relatively low rate of comorbidities in the study population.

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Methods	Results	Limitations and Interpretation
CONTAIN: Double-Blind RCT of Inhaled and Intranasal Ciclesonide in Nonhospitalized Patients With COVID-19[4]		
Key Inclusion Criteria: • Aged ≥18 years • Positive SARS-CoV-2 molecular diagnostic test result • ≥1 symptom of fever, cough, or shortness of breath • Symptom duration ≤6 days **Key Exclusion Criteria:** • Already taking an inhaled corticosteroid or taken PO or IM corticosteroids within 7 days of enrollment • Unable to use an inhaler • No respiratory symptoms • Use of oxygen at home • COVID-19 vaccinated **Interventions:** • Ciclesonide MDI 600 µg/actuation and intranasal ciclesonide 100 µg, both twice a day for 14 days (n = 105) • Saline placebo MDI and intranasal saline, both twice a day for 14 days (n = 98) **Primary Endpoint:** • Resolution of fever and all respiratory symptoms at Day 7 **Key Secondary Endpoints:** • Resolution of fever and all respiratory symptoms at Day 14 • Hospital admission by Day 14	**Participant Characteristics:** • Median age 35 years; 54% women; 61% White • 20% with comorbid condition **Primary Outcome:** • Percentage of patients with resolution of fever and all respiratory symptoms at Day 7: 40% in ciclesonide arm vs. 35% in placebo arm (adjusted risk difference 5.5%; 95% CI, -7.8% to 18.8%). **Secondary Outcomes:** • Percentage of patients with resolution of fever and all respiratory symptoms at Day 14: 66% in ciclesonide arm vs. 58% in placebo arm (adjusted risk difference 7.5%; 95% CI, -5.9% to 20.8%). • Percentage of patients who were admitted to the hospital by Day 14: 6% in ciclesonide arm vs. 3% in placebo arm (adjusted risk difference 2.3%; 95% CI, -3.0% to 7.6%).	**Key Limitation:** • Small study with a relatively young, healthy population **Interpretation:** • The use of inhaled ciclesonide plus intranasal ciclesonide did not improve resolution of fever and respiratory symptoms in nonhospitalized patients with COVID-19.

Key: BMI = body mass index; CVD = cardiovascular disease; DM = diabetes mellitus; ED = emergency department; HTN = hypertension; IM = intramuscular; MDI = metered dose inhaler; the Panel = the COVID-19 Treatment Guidelines Panel; PCR = polymerase chain reaction; PO = oral; RCT = randomized controlled trial; RT-PCR = reverse transcription polymerase chain reaction

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Fluvoxamine

Last Updated: December 16, 2021

Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) that is approved by the Food and Drug Administration (FDA) for the treatment of obsessive-compulsive disorder and is used for other conditions, including depression. Fluvoxamine is not FDA-approved for the treatment of any infection.

Anti-Inflammatory Effect of Fluvoxamine and Rationale for Use in COVID-19

In a murine sepsis model, fluvoxamine was found to bind to the sigma-1 receptor on immune cells, resulting in reduced production of inflammatory cytokines.[1] In an in vitro study of human endothelial cells and macrophages, fluvoxamine reduced the expression of inflammatory genes.[2] Ongoing studies are establishing whether the anti-inflammatory effects of fluvoxamine observed in nonclinical studies also occur in humans and are clinically relevant in the setting of COVID-19.

Recommendation

- There is insufficient evidence for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of fluvoxamine for the treatment of COVID-19.

Rationale

Three randomized trials have studied the use of fluvoxamine for the treatment of nonhospitalized patients with COVID-19. In STOP COVID, a contactless, double-blind randomized placebo-controlled trial conducted in the United States among nonhospitalized adults with mild COVID-19 diagnosed within 7 days of symptom onset, fluvoxamine (100 mg up to 3 times daily for 15 days) reduced clinical deterioration at Day 15.[3] Clinical deterioration was defined as shortness of breath plus oxygen saturation (SpO_2) <92% or hospitalization plus SpO_2 <92%. This was a small study (≤80 participants per arm) with limited cases of clinical deterioration and a short follow-up period. In addition, 24% of participants stopped responding to surveys prior to Day 15.

The subsequent STOP COVID 2, a Phase 3 randomized controlled trial (ClinicalTrials.gov Identifier NCT04668950) that enrolled >700 participants in the United States and Canada, was stopped for futility by a data safety monitoring board after lower than expected case rates and treatment effect were observed.[4]

TOGETHER is an adaptive platform, double-blind randomized placebo-controlled trial conducted in Brazil.[5] Nonhospitalized adults with COVID-19 and a known risk factor for progression to severe disease were randomized to fluvoxamine 100 mg twice daily (n = 741) or placebo (n = 756) for 10 days. Fluvoxamine use was associated with a lower risk of the primary composite outcome of retention in the emergency department for >6 hours or admission to a tertiary hospital (79 of 741 participants [11%] in the fluvoxamine arm vs. 119 of 756 participants [16%] in the placebo arm [relative risk 0.68; 95% CrI, 0.52–0.88]). Of note, 87% of the primary outcome events were hospitalizations. There was no statistically significant difference between study arms for the secondary outcomes of need for hospitalization or time to symptom resolution. There was no significant difference in mortality between study arms in the intention-to-treat (ITT) population (17 of 741 participants [2%] in the fluvoxamine arm vs. 25 of 756 participants [3%] in the placebo arm [OR 0.69; 95% CI, 0.36–1.27]). In a secondary, per-protocol analysis of participants who received >80% of possible doses, death was the outcome for 1 of 548 participants (<1%) in the fluvoxamine arm versus 12 of 618 participants (2%) in the placebo arm (OR 0.09; 95% CI, 0.01–0.47). Participants in the fluvoxamine arm were less likely to present to an emergency setting for COVID-19 for any duration, although this analysis was not prespecified.

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Compared with those in the placebo arm, participants who received fluvoxamine were less adherent to therapy and discontinued therapy due to intolerance more often.

While fluvoxamine treatment significantly reduced the primary composite outcome in the TOGETHER trial (i.e., retention in the emergency department for >6 hours or admission to a tertiary hospital), the difference in hospitalizations between arms was not significant.[5] Defining the clinical relevance of the >6 hour emergency department observation time endpoint is difficult, especially its applicability to practice settings in different countries. Moreover, the endpoint has not been used in other studies of interventions for nonhospitalized patients at high risk for hospitalization and death. While a per-protocol analysis found a significant treatment effect for mortality in patients taking >80% of possible doses (assessed by patient self-report), no such benefit was found in the primary ITT analysis. The 80% threshold has no clear justification, and only 74% of participants in the fluvoxamine arm reached this level of adherence. Since per-protocol analyses are not randomized comparisons, they can introduce bias when adherence is associated with factors that influence the outcome; this bias cannot be excluded in this study. Notably, mortality in the placebo arm was substantially higher in those with ≤80% adherence than in those with >80% adherence, suggesting that factors other than adherence differed in the per-protocol population. Finally, including only participants who could tolerate fluvoxamine does not reflect the actual effectiveness of the drug, since intolerance and adherence appeared to be related.

Additional studies are needed to provide more specific, evidence-based guidance on the role of fluvoxamine for the treatment of COVID-19. Further details of the studies discussed are provided in Table 4c.

Adverse Effects, Monitoring, and Drug-Drug Interactions

When fluvoxamine is used to treat psychiatric conditions, the most common adverse effect is nausea, but adverse effects can include other gastrointestinal effects (e.g., diarrhea, indigestion), neurologic effects (e.g., asthenia, insomnia, somnolence, anxiety, headache), and rarely suicidal ideation.

Fluvoxamine is a cytochrome P450 (CYP) 2D6 substrate and a potent inhibitor of CYP1A2 and CYP2C19 and a moderate inhibitor of CYP2C9, CYP2D6, and CYP3A4.[6] Fluvoxamine can enhance the serotonergic effects of other SSRIs or monoamine oxidase inhibitors (MAOIs), resulting in serotonin syndrome; therefore, it should not be used within 2 weeks of receipt of other SSRIs or MAOIs. Fluvoxamine may enhance the anticoagulant effects of antiplatelets and anticoagulants; therefore, patients receiving these drugs should be closely monitored.

Considerations in Pregnancy

Fluvoxamine is not thought to increase the risk of congenital abnormalities; however, the data on its use in pregnancy are limited.[7,8] The association of SSRI use in the late third trimester with a small, increased risk of primary persistent pulmonary hypertension in newborns has not been excluded, although the absolute risk is likely low.[9] The risk of fluvoxamine use in pregnancy for the treatment of COVID-19 should be balanced with the potential benefit.

Considerations in Children

Fluvoxamine is approved by the FDA for the treatment of obsessive-compulsive disorder in children aged ≥8 years.[10] Adverse effects due to SSRI use seen in children are similar to those seen in adults, although children and adolescents appear to have higher rates of behavioral activation and vomiting than adults.[11] There are no data on the use of fluvoxamine for the prevention or treatment of COVID-19 in children.

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Clinical Trials

See ClinicalTrials.gov for the latest information on studies of fluvoxamine and COVID-19.

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Table 4c. Fluvoxamine: Selected Clinical Data

Last Updated: December 16, 2021

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

Methods	Results	Limitations and Interpretation
TOGETHER: Double-Blind, Adaptive RCT of Fluvoxamine in Nonhospitalized Patients With COVID-19 in Brazil[1]		
Key Inclusion Criteria: • Aged ≥50 years or aged ≥18 years with comorbidities • Laboratory-confirmed SARS-CoV-2 infection • ≤7 days of symptoms **Key Exclusion Criteria:** • Use of an SSRI • Severe mental illness • Cirrhosis, recent seizures, severe ventricular cardia arrythmia **Interventions:** • Fluvoxamine 100 mg PO twice daily for 10 days (n = 741) • Placebo (route, dosing frequency, and duration for some patients may have differed from fluvoxamine) (n = 756) **Primary Endpoint:** • Composite endpoint of emergency setting observation for >6 hours or hospitalization due to progression of COVID-19 within 28 days after randomization **Key Secondary Endpoints:** • Occurrence of COVID-19-related hospitalizations • Time to symptom resolution • Proportion of patients who were adherent to study drugs, defined as receiving >80% of possible doses	**Participant Characteristics:** • Median age 50 years; 58% women; 95% self-identified as mixed race • 13% with uncontrolled HTN; 13% with type 2 DM; 50% with BMI ≥30 kg/m^2 • Mean of 3.8 days from symptom onset to randomization **Primary Outcome:** • Proportion of patients who met the primary composite endpoint: 11% in fluvoxamine arm vs. 16% in placebo arm (relative risk 0.68; 95% CrI, 0.52–0.88) **Secondary Outcomes:** • 87% of clinical events were hospitalizations. • No difference between arms in COVID-19-related hospitalizations: 10% in fluvoxamine arm vs. 13% in placebo arm (OR 0.77; 95% CI, 0.55–1.05) • No difference between arms in time to symptom resolution. • Adherence: 74% in fluvoxamine arm vs. 82% in placebo arm (OR 0.62; 95% CI, 0.48–0.81). 11% in fluvoxamine arm vs. 8% in placebo arm stopped drug due to issues of tolerability. • Mortality (ITT): 2% in fluvoxamine arm vs. 3% in placebo arm (OR 0.68; 95% CI, 0.36–1.27)	**Key Limitations:** • The >6-hour emergency setting observation endpoint has not been used in other studies of interventions for nonhospitalized patients who are at high risk for hospitalization and death • As this was an adaptive platform trial where multiple investigational treatments or placebos were being evaluated simultaneously, not all patients in the placebo arm received a placebo that was matched to fluvoxamine by route of administration, dosing frequency, or duration of therapy • PP analyses are not randomized comparisons, and they introduce bias when adherence is associated with factors that influence the outcome • Adherence was self-reported and not verified **Interpretation:** • Fluvoxamine reduced the proportion of patients who met the composite endpoint of COVID-19-related hospitalization or retention in an emergency setting for >6 hours. • The use of fluvoxamine did not impact the incidence of COVID-19-related hospitalizations.

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Methods	Results	Limitations and Interpretation
TOGETHER: Double-Blind, Adaptive RCT of Fluvoxamine in Nonhospitalized Patients With COVID-19 in Brazil[1], continued		
• Mortality in both the primary ITT population and a PP population that included patients who took >80% of the study medication doses	• Mortality (PP): <1% in fluvoxamine arm vs. 2% in placebo arm (OR 0.09; 95% CI, 0.01–0.47)	• It is difficult to define the clinical relevance of the >6-hour emergency setting observation endpoint and apply it to practice settings in different countries. • Fluvoxamine did not have a consistent impact on mortality. • Fluvoxamine did not impact time to symptom resolution.
STOP COVID: Double-Blind RCT of Fluvoxamine in Nonhospitalized Patients With COVID-19 in the United States[2]		

Key Inclusion Criteria:
• Aged ≥18 years
• Positive SARS-CoV-2 PCR result
• ≤7 days of symptoms
Key Exclusion Criteria:
• Immunocompromised
• Unstable medical comorbidities
Interventions:
• Fluvoxamine 50 mg PO for 1 dose, then fluvoxamine 100 mg twice daily, then fluvoxamine 100 mg 3 times daily through Day 15 (n = 80)
• Placebo (n = 72)
Primary Endpoint:
• Clinical deterioration within 15 days of randomization. Clinical deterioration was defined as:
  • Having dyspnea or being hospitalized for dyspnea or pneumonia; *and*
  • Having SpO_2 <92% on room air or requiring supplemental oxygen to attain SpO_2 ≥92%
Key Secondary Endpoint:
• Hospitalization
	Participant Characteristics:
	• Mean age 46 years; 72% women; 25% Black
	• 56% with obesity; 20% with HTN; 17% with asthma
	• Median of 4 days from symptom onset to randomization
	Primary Outcome:
	• Clinical deterioration: 0% in fluvoxamine arm vs. 8.3% in placebo arm (absolute difference 8.7%; 95% CI, 1.8% to 16.4%)
	Secondary Outcome:
	• No patients in fluvoxamine arm and 4 patients in placebo arm were hospitalized.
		Key Limitations:
		• Small sample size
		• Short follow-up period
		• Ascertaining clinical deterioration was challenging because all assessments were done remotely
		• 24% of patients stopped responding to follow-up prior to Day 15 but were included in the final analysis
		Interpretation:
		• Fluvoxamine reduced the proportion of patients who experienced clinical deterioration.
		• Due to significant limitations, it is difficult to draw definitive conclusions about the efficacy of using fluvoxamine to treat COVID-19.

Key: BMI = body mass index; DM = diabetes; HTN = hypertension; ITT = intention-to-treat; the Panel = the COVID-19 Treatment Guidelines Panel; PCR = polymerase chain reaction; PO = oral; PP = per protocol; RCT = randomized controlled trial; SpO_2 = oxygen saturation; SSRI = selective serotonin reuptake inhibitor

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Granulocyte-Macrophage Colony-Stimulating Factor Inhibitors

Last Updated: March 24, 2022

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a myelopoietic growth factor and pro-inflammatory cytokine that plays a central role in a broad range of immune-mediated diseases. GM-CSF, which is secreted by macrophages, T cells, mast cells, natural killer cells, endothelial cells, and fibroblasts, regulates macrophage number and function. It acts as a pro-inflammatory signal, prompting macrophages to launch an immune cascade that ultimately results in tissue damage.[1,2] GM-CSF is believed to be a key driver of lung inflammation in severe and critical COVID-19 pneumonia, operating upstream of other pro-inflammatory cytokines and chemokines.[1-6] Anti-GM-CSF monoclonal antibodies (mAbs) may mitigate inflammation by inhibiting this signaling axis upstream and thus minimizing downstream production of numerous pro-inflammatory mediators involved in the pathogenesis of COVID-19.[7] Gimsilumab, lenzilumab, namilumab, and otilimab target GM-CSF directly, neutralizing the biological function of GM-CSF by blocking the interaction of GM-CSF with its cell surface receptor.[1,8,9] Mavrilimumab targets the alpha subunit of the GM-CSF receptor, blocking intracellular signaling of GM-CSF.[8,10] None of these agents are currently FDA approved for any indication.

Recommendation

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

Rationale

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

Clinical Data for COVID-19

Lenzilumab, mavrilimumab, namilumab, and otilimab have been evaluated in clinical trials in hospitalized adults with SARS-CoV-2 pneumonia.[12-15] Clinical data are not yet published for gimsilumab. The Panel's recommendations are based on the results of the available clinical studies. Selected clinical data on the use of anti-GM-CSF mAbs for the treatment of COVID-19 are summarized in Table 4d.

Clinical Trials

See ClinicalTrials.gov for a list of ongoing clinical trials that are evaluating the use of GM-CSF

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inhibitors for the treatment of COVID-19.

Adverse Effects

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

Considerations in Pregnancy

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

Considerations in Children

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

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Table 4d. Granulocyte-Macrophage Colony-Stimulating Factor Inhibitors: Selected Clinical Data

Last Updated: March 24, 2022

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

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

Methods	Results	Limitations and Interpretation
LIVE-AIR: Double-Blind RCT of Lenzilumab in Hospitalized Patients With Severe COVID-19 Pneumonia in the United States and Brazil[1,2]		
Key Inclusion Criteria: • Hospitalized with SARS-CoV-2 pneumonia • SpO_2 ≤94% on room air or required low-flow supplemental oxygen, HFNC oxygen, or NIV **Key Exclusion Criteria:** • MV or ECMO • Bacterial pneumonia, fungal or viral infection • 48-hour survival not expected • Use of IL-1 inhibitors, IL-6 inhibitors, kinase inhibitors, or mAbs within prior 8 weeks **Interventions:** • 3 doses of lenzilumab 600 mg IV 8 hours apart (n = 236) • Placebo (n = 243) **Primary Endpoint:** • Survival without MV through Day 28 **Key Secondary Endpoints:** • Mortality • Incidence of death or requiring MV or ECMO **Exploratory Endpoint:** • Survival without MV, stratified by baseline CRP	**Participant Characteristics:** • Mean age 61 years; 65% men; 72% White • 55% BMI ≥30 • At baseline: 41% received HFNC oxygen or NIV • 94% received corticosteroids; 72% received RDV; 69% received corticosteroids and RDV • Median CRP 79 mg/L **Primary Outcome:** • Survival without MV through Day 28: 84% in lenzilumab arm vs. 78% in placebo arm (HR 1.54; 95% CI, 1.02–2.32; $P = 0.040$) **Key Secondary Outcomes:** • Mortality: 10% in lenzilumab arm vs. 14% in placebo arm (HR 0.72; 95% CI, 0.42–1.23; $P = 0.24$) • Incidence of death or requiring MV or ECMO: 15% in lenzilumab arm vs. 21% in placebo arm (HR 0.67; 95% CI, 0.41–1.10; $P = 0.11$) **Exploratory Outcome:** • Survival without MV for baseline CRP <150 mg/L: 90% in lenzilumab arm vs. 79% in placebo arm (HR 2.54; 95% CI, 1.46–4.41; $P = 0.0009$)	**Key Limitations:** • Not powered to detect a survival benefit • Access to supportive care differed across study sites **Interpretation:** • Lenzilumab improved ventilator-free survival in participants with hypoxemia who were not receiving MV, with the greatest benefit among those with lower CRP levels.

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Methods	Results	Limitations and Interpretation
MASH-COVID: Double-Blind RCT of Mavrilimumab in Hospitalized Patients With Severe COVID-19 Pneumonia and Systemic Hyperinflammation in the United States[3]		

Key Inclusion Criteria:
• Hospitalization with SARS-CoV-2 pneumonia
• SpO_2 <92% on room air or required supplemental oxygen
• CRP >5 mg/dL
Key Exclusion Criteria:
• MV
• ANC <1,500/mm^3
• Uncontrolled bacterial infection
Interventions:
• Mavrilimumab 6 mg/kg as single IV infusion (n = 21)
• Placebo (n = 19)
Primary Endpoint:
• Alive and off supplemental oxygen at Day 14
Key Secondary Endpoints:
• Mortality at Day 28
• Alive without respiratory failure at Day 28
	Participant Characteristics:
	• Median age 57 years; 65% men; 40% African American
	• At baseline:
	  • 50% required HFNC oxygen or NIV
	  • 65% received corticosteroids
	  • 75% received RDV
	Primary Outcome:
	• Alive and off supplemental oxygen at Day 14: 57% in mavrilimumab arm vs. 47% in placebo arm (OR 1.48; 95% CI, 0.43–5.16; *P* = 0.76)
	Key Secondary Outcomes:
	• Mortality at Day 28: 1 (5%) in mavrilimumab arm vs. 3 (16%) in placebo arm (HR 3.72; 95% CI, 0.39–35.79; *P* = 0.22)
	• Alive without respiratory failure at Day 28: 95% in mavrilimumab arm vs. 79% in placebo arm (OR 5.33; 95% CI, 0.54–52.7; *P* = 0.43)
		Key Limitations:
		• Very small sample size
		• Ended early due to slow enrollment
		Interpretation:
		• Among participants with systemic hyperinflammation and severe COVID-19 pneumonia, there was no evidence that use of mavrilimumab improved supplemental oxygen–free survival by Day 14.

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Methods	Results	Limitations and Interpretation
OSCAR: Double-Blind RCT of Otilimab in Patients With Severe COVID-19 Pneumonia in 17 Countries[4]		

Key Inclusion Criteria:
• Hospitalized with SARS-CoV-2 pneumonia
• Required HFNC oxygen, NIV, or MV ≤48 hours before dosing
• CRP or ferritin >ULN
Key Exclusion Criteria:
• Death likely <48 hours
• Multiple organ failure
• SOFA score >10 if in ICU
• ECMO
• Dialysis
• High-dose noradrenaline (>0.15 ug/kg/min) or equivalent
• >1 vasopressor
Interventions:
• Otilimab 90 mg IV as single infusion (n = 395)
• Placebo (n = 398)
Primary Endpoint:
• Alive and free of respiratory failure at Day 28
Key Secondary Endpoint:
• All-cause mortality at Day 60
	Participant Characteristics:
	• Mean age 59 years; 72% men; 66% White
	• At baseline:
	  • 77% received HFNC oxygen or NIV; 22% received MV
	  • 83% received corticosteroids; 34% received RDV
	Primary Outcome:
	• Alive and free of respiratory failure at Day 28: 71% in otilimab arm vs. 67% in placebo arm (model-adjusted difference 5.3%; 95% CI, -0.8 to 11.4; *P* = 0.09)
	Key Secondary Outcome:
	• All-cause mortality at Day 60: 23% in otilimab arm vs. 24% in placebo arm (model-adjusted difference -2.4%; 95% CI, -8.0 to 3.3; *P* = 0.41)
		Key Limitations:
		• Changes in SOC during study may have affected outcomes.
		Interpretation:
		• For participants with severe COVID-19 pneumonia, use of otilimab did not significantly reduce the probability of respiratory failure or death.

Key: ANC = absolute neutrophil count; BMI = body mass index; CRP = C-reactive protein; ECMO = extracorporeal membrane oxygenation; GM-CSF = granulocyte-macrophage colony-stimulating factor; HFNC = high-flow nasal cannula; ICU = intensive care unit; IL = interleukin; IV = intravenous; mAb = monoclonal antibody; MV = mechanical ventilation; NIV = noninvasive ventilation; RCT = randomized controlled trial; RDV = remdesivir; SOC = standard of care; SOFA = sequential organ failure assessment; SpO_2 = oxygen saturation; ULN = upper limit of normal

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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 acute 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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Interleukin-1 Inhibitors

Last Updated: October 19, 2021

Endogenous interleukin (IL)-1 is elevated in patients with COVID-19.[1,2] In addition, SARS-CoV-2 infection causes epithelial damage that leads to the release of IL-1 beta, which recruits inflammatory cells and induces the release of IL-1 beta in monocytes. This in turn leads to the release of more IL-1 to recruit and activate additional innate immune cells. Drugs that block the IL-1 receptor (e.g., anakinra) or drugs that block IL-1 signaling (e.g., canakinumab) can potentially interrupt this autoinflammatory loop. These drugs are being investigated as potential treatments for 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.[3] It is used off-label to treat severe chimeric antigen receptor T cell-mediated cytokine release syndrome and macrophage activation syndrome (MAS)/secondary hemophagocytic lymphohistiocytosis.

Canakinumab is a human monoclonal antibody that targets the beta subunit of IL-1 and is approved by the FDA for the treatment of systemic juvenile idiopathic arthritis and Still's disease.

Recommendations

- There is insufficient evidence for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of anakinra for the treatment of COVID-19.
- The Panel **recommends against** the use of **canakinumab** for the treatment of COVID-19, except in a clinical trial **(BIIa)**.

Rationale

In the SAVE-MORE trial, 594 hospitalized patients who had moderate or severe COVID-19 pneumonia and plasma-soluble urokinase plasminogen activator receptor (suPAR) levels ≥6 ng/mL were randomized to receive either anakinra or placebo. The study found that patients who received anakinra had a lower risk of clinical progression of COVID-19 than those who received placebo.[4] CORIMUNO-ANA-1, a randomized controlled trial that compared the use of anakinra to usual care in 116 hospitalized patients who were hypoxemic but did not require high-flow oxygen or ventilation, was stopped early for futility.[5] REMAP-CAP, an open-label, adaptive platform, randomized controlled trial that evaluated several immunomodulators in patients with COVID-19 who required organ support, found that anakinra was not effective in reducing the combined endpoint of in-hospital mortality and days of organ support.[6] Although the SAVE-MORE study suggests that suPAR levels could be used in risk stratification to identify populations that could benefit from IL-1 inhibition, the laboratory assay that is used to assess suPAR levels is not currently available in many countries, including the United States. After reviewing the results of the studies discussed above and taking into consideration the fact that suPAR assays are not widely available to guide the use of anakinra, the Panel has concluded that there is insufficient evidence to recommend either for or against the use of anakinra for the treatment of COVID-19 in hospitalized patients.

Finally, CAN-COVID, a randomized controlled trial that evaluated canakinumab in hospitalized patients with COVID-19 who were hypoxemic but did not require ventilatory support, reported that the use of canakinumab did not improve the likelihood of survival without invasive mechanical ventilation.[7] Because of these results, the Panel **recommends against** the use of **canakinumab** for the treatment of COVID-19, except in a clinical trial **(BIIa)**.

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Clinical Data for COVID-19

SAVE-MORE

SAVE-MORE was a randomized controlled trial in 594 hospitalized patients with moderate or severe COVID-19 pneumonia and plasma suPAR levels ≥6 ng/mL. Patients who required noninvasive or invasive mechanical ventilation were excluded from the study. Patients were randomized 2:1 to receive anakinra 100 mg subcutaneously once daily for 10 days or placebo. The primary endpoint was clinical status at Day 28 on the 11-point World Health Organization Clinical Progression Scale (WHO-CPS).[4]

Results

- Patients who were randomized to receive anakinra had a lower odds of progression of COVID-19 on the WHO-CPS (OR 0.36; 95% CI, 0.26–0.50; $P < 0.0001$).
- The secondary endpoints also favored anakinra, including the absolute decrease in WHO-CPS scores from baseline at Days 14 and 28, the absolute decrease in Sequential Organ Failure Assessment scores from baseline at Day 7, the median time to hospital discharge, and the median duration of intensive care unit (ICU) stays.
- A smaller proportion of patients in the anakinra arm experienced secondary infections, including ventilator-associated pneumonias, than in the placebo arm (8.4% vs. 15.9%; $P = 0.01$).
- Twenty-eight-day mortality was lower among patients who received anakinra than those who received placebo (3.2% vs. 6.9%; HR 0.45; 95% CI, 0.21–0.98; $P = 0.045$).

Limitations

- The laboratory assay that is used to assess suPAR levels is not currently available in many countries, including the United States.

REMAP-CAP

The REMAP-CAP trial is an open-label, adaptive platform trial in which eligible participants are randomized to several domains, including the Immune Modulation Therapy domain, which consists of two IL-6 inhibitors, anakinra, interferon beta-1a, and a control group. Participants are eligible for enrollment if they are within 24 hours of receiving respiratory or cardiovascular organ support in the ICU and they have suspected or microbiologically confirmed COVID-19.

Anakinra 300 mg was given intravenously (IV) as a loading dose, followed by anakinra 100 mg IV every 6 hours for 14 days until patients were either free from invasive mechanical ventilation for >24 hours or discharged from the ICU. The primary outcome was measured using an ordinal scale that included a composite of in-hospital mortality and duration of respiratory and cardiovascular organ support at 21 days; all deaths up to 90 days were assigned the worst outcome. The trial used a Bayesian design that allowed the authors to compare nonconcurrently randomized interventions across time periods.[6]

Results

- Of the 2,274 participants who were randomized to one of the arms in the Immune Modulation Therapy domain, 365 individuals were assigned to receive anakinra and included in the analysis, 406 were assigned to the usual care (control) arm, 943 were assigned to receive tocilizumab, and 483 were assigned to receive sarilumab.
- Of those assigned to receive anakinra, 37% were receiving invasive mechanical ventilation at study entry compared with 32% of patients in the other arms. The other patients received oxygen through a high-flow nasal cannula or noninvasive ventilation, with a few exceptions.
- The median number of organ support-free days was similar for patients who received anakinra and

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those who received usual care (0 days [IQR 1–15 days] vs. 0 days [IQR -1 to 15 days]). The aOR for organ support-free days was 0.99 for anakinra (95% CrI, 0.74–1.35), with a 46.6% posterior probability of superiority to control. Sixty percent of those who were assigned to receive anakinra survived compared to 63% of those who were assigned to the control arm, with a 43.6% posterior probability that anakinra was superior to usual care.

- The risk of experiencing serious adverse events was similar between the arms.

Limitations

- Patients were not randomized contemporaneously to receive anakinra or usual care; the treatment effect was estimated from an overarching model that mostly included patients who were randomized to receive an IL-6 inhibitor (tocilizumab or sarilumab) or usual care, and patients who were randomized to receive an IL-6 inhibitor or anakinra. Thus, the estimate of the treatment effect is not fully protected by randomization.
- This study had an open-label design.

CORIMUNO-ANA-1

The CORIMUNO-ANA-1 trial randomized 116 hospitalized patients with COVID-19 pneumonia 1:1 to receive either usual care plus anakinra (200 mg IV twice a day on Days 1–3, 100 mg IV twice on Day 4, and 100 mg IV once on Day 5) or usual care alone. Patients were eligible for enrollment if they had laboratory-confirmed SARS-CoV-2 infection with COVID-19 pneumonia and they required >3 L/min of supplemental oxygen. Patients who required high-flow oxygen, ventilation, or ICU admission were excluded. The two coprimary outcomes were the proportion of patients who had died or who needed noninvasive or invasive mechanical ventilation by Day 4 (score of >5 on the WHO-CPS) and the proportion who survived without the need for noninvasive or invasive mechanical ventilation (including high-flow oxygen) by Day 14.[5]

Results

- There was no difference between the anakinra plus usual care arm and the usual care alone arm in the two coprimary outcomes: by Day 4, 36% of patients in the anakinra arm had died or required high-flow oxygen or ventilation compared with 38% in the usual care arm (90% CrI, -17.1 to 12.0, posterior probability of benefit 61%). By Day 14, 47% of patients in the anakinra arm had died or required noninvasive or invasive mechanical ventilation compared to 51% in the usual care arm (median HR 0.97; 90% CrI, 0.62–1.52; posterior probability of benefit 55%).
- Fifty-two percent of patients received corticosteroids at study entry.
- Serious adverse events occurred in 46% of patients in the anakinra arm compared to 38% in the usual care arm; 11 of 59 patients (18.6%) in the anakinra arm experienced bacterial or fungal infections compared to 4 of 55 patients (7.3%) who received usual care.

Limitations

- The limitations of this study include the small sample size, narrow eligibility criteria, and the fact that many patients did not receive current standard-of-care therapy (e.g., corticosteroids, remdesivir).

CAN-COVID

CAN-COVID was a double-blind, placebo-controlled randomized trial of 454 hospitalized patients with COVID-19 who were hypoxemic but not mechanically ventilated and had elevated C-reactive protein (≥ 20 mg/L) or ferritin (≥600 micrograms/L) levels. Patients were randomized 1:1 to receive a single dose of IV canakinumab (450 mg for a body weight of 40 kg to <60 kg, 600 mg for 60–80 kg, and 750

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mg for >80 kg) or placebo. The primary outcome was survival without the need for invasive mechanical ventilation from Days 3 through 29.[7]

Results

- There was no statistical difference between the canakinumab arm and placebo arm in the proportion of patients who survived without invasive mechanical ventilation (88.8% vs. 85.7%; $P = 0.29$).
- The number of COVID-19-related deaths at 4 weeks was similar for the two arms (11 of 223 patients [4.9%] in the canakinumab arm vs. 16 of 222 patients [7.2%] in the placebo arm; OR 0.67; 95% CI, 0.30–1.50).
- Forty-one percent of patients in the canakinumab arm and 32% in the placebo arm received dexamethasone.
- Serious adverse events occurred in 16% of patients who received canakinumab and in 20.6% of patients who received placebo.

Limitations

- The use of corticosteroids was unbalanced in this study, with more patients receiving dexamethasone at baseline in the canakinumab arm than in the placebo arm.
- More patients received dexamethasone after the trial was underway in the placebo arm than in the canakinumab arm (22.5% vs. 14.5%), and more patients received tocilizumab in the placebo arm than in the canakinumab arm (8.8% vs. 2.2%).

Other small cohort studies, case-control studies, and case series have reported mixed findings with regard to improvement in outcomes among patients who received anakinra for the treatment of COVID-19.[8-11] The clinical implication of these findings is uncertain due to small sample sizes and unmeasured confounding factors. Therefore, these studies did not substantially influence the Panel's current recommendations for using IL-1 inhibitors.

Clinical Trials

See ClinicalTrials.gov for a list of clinical trials that are evaluating anakinra and canakinumab for the treatment of COVID-19.

Adverse Effects

Headache, nausea, vomiting, and liver enzyme elevations can occur with both anakinra and canakinumab.

Anakinra was not associated with any significant safety concerns when used in clinical trials for the treatment of sepsis.[12-14] Increased rates of infection were reported with prolonged anakinra use in combination with tumor necrosis factor-alpha blockade, but not with short-term use.[15]

Considerations in Pregnancy

The data on using IL-1 inhibitors to treat COVID-19 in pregnant patients are currently limited. The American College of Rheumatology recommends against the use of anakinra during pregnancy.[16] Unintentional first-trimester exposure to anakinra is unlikely to be harmful, given the minimal transfer of monoclonal antibodies across the placenta early in pregnancy.[17]

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Considerations in Children

Anakinra has been used in the treatment of severely ill children with rheumatologic conditions, including MAS. The data on the use of anakinra in pediatric patients with acute respiratory distress syndrome or sepsis are limited. Anakinra is rarely used to treat pediatric patients with acute COVID-19, and it has been used in approximately 10% of cases of multisystem inflammatory syndrome in children (MIS-C).[18,19] Anakinra is often included in institutional protocols for the treatment of MIS-C in the United States, and it is mentioned as an option for second-line therapy for refractory MIS-C in national consensus guidelines.[20-22] However, robust data on the effectiveness of anakinra for the treatment of MIS-C are not currently available. Data on using canakinumab in pediatric patients are limited to use in patients with periodic fever syndromes and systemic juvenile idiopathic arthritis. There are no data on its use in pediatric patients with acute COVID-19 or MIS-C. The Panel recommends consulting with a multidisciplinary team when using immunomodulating therapy (which may include anakinra) in children with MIS-C **(AIII)**.

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Interleukin-6 Inhibitors

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Interleukin (IL)-6 is a pleiotropic, proinflammatory cytokine produced by a variety of cell types, including lymphocytes, monocytes, and fibroblasts. Infection by SARS-CoV induces a dose-dependent production of IL-6 from bronchial epithelial cells.[1] COVID-19-associated systemic inflammation and hypoxemic 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 IL-6 levels or the effects of IL-6 may reduce the duration and/or severity of COVID-19.

There are 2 classes of Food and Drug Administration (FDA)-approved IL-6 inhibitors: anti-IL-6 receptor monoclonal antibodies (mAbs) (e.g., sarilumab, tocilizumab) and anti-IL-6 mAbs (i.e., siltuximab). These drugs have been evaluated in patients with COVID-19 who have systemic inflammation.

Recommendations

- See Therapeutic Management of Hospitalized Adults With COVID-19 for the COVID-19 Treatment Guidelines Panel's (the Panel) recommendations on the use of IL-6 inhibitors (e.g., sarilumab, tocilizumab) in hospitalized patients who require supplemental oxygen, high-flow oxygen, noninvasive ventilation (NIV), or mechanical ventilation.
- The Panel **recommends against** the use of anti-IL-6 mAb therapy (i.e., **siltuximab**) for the treatment of COVID-19, except in a clinical trial **(BIII)**.

Additional Considerations

- Tocilizumab and sarilumab **should be used with caution** in patients with COVID-19 who have not been adequately represented in clinical trials. This includes patients who are significantly immunosuppressed, particularly those who have recently received other biologic immunomodulating drugs, and patients with any of the following:
  - Alanine transaminase levels >5 times the upper limit of normal
  - A high risk for gastrointestinal perforation
  - An uncontrolled serious bacterial, fungal, or non-SARS-CoV-2 viral infection
  - Absolute neutrophil counts <500 cells/µL
  - Platelet counts <50,000 cells/µL
  - Known hypersensitivity to tocilizumab or sarilumab
- Tocilizumab and sarilumab should only be given in combination with a course of dexamethasone (or an alternative corticosteroid at a dose that is equivalent to dexamethasone 6 mg). See the Corticosteroids section for more information.
- Some clinicians may assess the patient's clinical response to dexamethasone before deciding whether tocilizumab or sarilumab is needed.
- In both the REMAP-CAP and the RECOVERY trials, 29% of patients received a second dose of tocilizumab at the discretion of their treating physician. However, there is currently insufficient evidence to recommend either for or against a second dose of tocilizumab.[5,6]
- Cases of severe and disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with tocilizumab and corticosteroids.[7,8] Many clinicians would initiate empiric treatment (e.g., with the antiparasitic drug ivermectin) with or without serologic testing in patients who are from areas where *Strongyloides* is endemic (i.e., tropical, subtropical, or warm temperate areas).[9]

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Rationale

The results of the RECOVERY and REMAP-CAP trials provide consistent evidence that tocilizumab, when coadministered with corticosteroids, offers a modest mortality benefit in certain patients with COVID-19 who are severely ill, who are rapidly deteriorating and have increasing oxygen needs, and who have a significant inflammatory response.[5,6] However, the Panel found it challenging to define the specific patient populations that would benefit from this intervention. If tocilizumab is not available, sarilumab may be used as an alternative because it has demonstrated a similar clinical benefit in improving survival and reducing the duration of organ support in the REMAP-CAP trial.[10] However, the Panel recommends **sarilumab** only when tocilizumab is not available or is not feasible to use **(BIIa)** because the evidence of efficacy for tocilizumab is more extensive than for sarilumab; in addition, sarilumab is currently only approved for use as a subcutaneous (SQ) injection in the United States.

The data on the efficacy of siltuximab in patients with COVID-19 are currently limited.[11]

Anti-Interleukin-6 Receptor Monoclonal Antibodies

Tocilizumab

Tocilizumab is a recombinant humanized anti-IL-6 receptor mAb that is approved by the FDA for use in patients with rheumatologic disorders and cytokine release syndrome induced by chimeric antigen receptor T cell (CAR T-cell) therapy. Tocilizumab can be dosed as an intravenous (IV) infusion or an SQ injection. The IV formulation should be used to treat cytokine release syndrome.[11]

Clinical Data for COVID-19

Clinical data on the use of tocilizumab (and other IL-6 inhibitors) for the treatment of COVID-19, including data from several randomized trials and large observational studies, are summarized in Table 4e.

The initial studies that evaluated the use of tocilizumab for the treatment of COVID-19 produced conflicting results. Many of these trials were limited by low power, heterogenous populations, and/or a low frequency of concomitant use of corticosteroids (now the standard of care for patients with severe COVID-19).[12-16]

Subsequently, in the setting of background corticosteroid therapy, the 2 largest randomized controlled trials evaluating tocilizumab, REMAP-CAP and RECOVERY, both reported a mortality benefit of tocilizumab in certain patients, including patients exhibiting rapid respiratory decompensation associated with an inflammatory response. REMAP-CAP enrolled critically ill patients who were within 24 hours of receiving respiratory support in an intensive care unit. The participants were randomized to receive open-label tocilizumab or usual care. In-hospital mortality was 28% in the tocilizumab arm and 36% in the usual care arm.[5] The RECOVERY trial enrolled hospitalized patients with COVID-19 into an open-label platform trial that included several treatment options.[6] A subset of all trial participants who had hypoxemia and CRP levels ≥75 mg/L were offered enrollment into a second randomization that evaluated tocilizumab versus usual care. In this subgroup, the 28-day mortality was 31% in the tocilizumab arm and 35% in the usual care arm. For additional findings from the REMAP-CAP and RECOVERY trials and the rationale for using tocilizumab in certain hospitalized patients who are exhibiting rapid respiratory decompensations due to COVID-19, see Therapeutic Management of Hospitalized Adults With COVID-19.

In contrast to the REMAP-CAP and RECOVERY trials, the REMDACTA trial did not find a mortality benefit of tocilizumab. The trial randomized hospitalized COVID-19 patients, most of whom required NIV or high-flow oxygen support, to receive tocilizumab or placebo. All the participants received

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remdesivir and most received corticosteroids. Tocilizumab use did not reduce 28-day mortality (18% in the tocilizumab arm and 20% in the placebo arm).[17]

Despite this conflicting evidence, the Panel's recommendations for using tocilizumab are based on the collective evidence from the clinical trials reported to date (see Table 4e).

Clinical Trials

See ClinicalTrials.gov for a list of clinical 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. In randomized trials, no excess secondary infections were seen among patients who received combination therapy compared to control patients. Additional adverse effects of tocilizumab, such as serious infections (e.g., tuberculosis [TB], bacterial or fungal infections) and bowel perforation, have been reported.[18]

Considerations in Pregnancy

There are insufficient data to determine whether there is a tocilizumab-associated risk for major birth defects or miscarriage. mAbs are actively transported across the placenta as pregnancy progresses (with the greatest transfer occurring during the third trimester), and this may affect immune responses in the exposed fetus. Given the paucity of data, current recommendations advise against the use of tocilizumab during pregnancy.[19] Whether to use tocilizumab during pregnancy should be a joint decision between the pregnant individual and their health care provider, and the decision-making process should include a discussion of the potential risks and benefits.

Considerations in Children

There are no systematic observational or randomized controlled trial data on the effectiveness of tocilizumab for the treatment of acute COVID-19 in pediatric patients or multisystem inflammatory syndrome in children (MIS-C). Tocilizumab has been used for children with cytokine release syndrome associated with CAR T-cell therapy and systemic and polyarticular juvenile idiopathic arthritis.[20] There is insufficient evidence for the Panel to recommend either for or against the use of tocilizumab in hospitalized children with COVID-19 or MIS-C.

Drug Availability

On June 24, 2021, the FDA issued an Emergency Use Authorization (EUA) for the use of tocilizumab in combination with corticosteroids in hospitalized adults and children aged ≥2 years with COVID-19 who require supplemental oxygen, NIV, mechanical ventilation, or extracorporeal membrane oxygenation.[20] Per this EUA, if a patient's clinical signs or symptoms worsen or do not improve after the first dose of tocilizumab, 1 additional infusion of tocilizumab may be administered at least 8 hours after the initial IV infusion. If there is a local or regional shortage of tocilizumab, sarilumab can be used as an alternative (see Therapeutic Management of Hospitalized Adults With COVID-19).[10]

Sarilumab

Sarilumab is a recombinant humanized anti-IL-6 receptor mAb that is approved by the FDA for use in patients with rheumatoid arthritis. It is available as an SQ formulation and is not approved for the treatment of cytokine release syndrome.

Clinical Data for COVID-19

The clinical data on the use of sarilumab as a treatment for COVID-19 are summarized in Table 4e.

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An adaptive Phase 2 and 3 double-blind randomized (2:2:1) placebo-controlled trial compared the efficacy and safety of sarilumab 400 mg IV and sarilumab 200 mg IV to placebo in hospitalized patients with COVID-19 (ClinicalTrials.gov Identifier NCT04315298). Results from this trial did not support a clinical benefit of sarilumab in hospitalized patients receiving supplemental oxygen.[21]

A similar adaptive design study in the United States in patients with severe and critical COVID-19 also failed to show a benefit of sarilumab. In this placebo-controlled trial, there was a reduction in mortality among the sarilumab recipients with critical COVID-19 pneumonia who required mechanical ventilation and received corticosteroids at baseline. However, due to the small sample size, this result was not statistically significant.[22] In the REMAP-CAP trial, the efficacy results for sarilumab were similar to those for tocilizumab. Compared to the patients in the standard of care arm (n = 418), those in the sarilumab arm (n = 485) had more organ support-free days (OR 1.50; 95% CrI, 1.13–2.00) and a greater likelihood of survival while hospitalized (OR 1.51; 95% CrI, 1.06–2.20). A notable limitation to the sarilumab findings in the REMAP-CAP trial is that patients in the standard of care arm were enrolled earlier in the pandemic than those in the sarilumab arm: randomization closed on November 2020 for the standard of care arm and continued through April 2021 for the sarilumab arm.[10]

Clinical Trials

See ClinicalTrials.gov for a list of clinical trials that are evaluating the use of sarilumab for the treatment of COVID-19.

Adverse Effects

The primary laboratory abnormalities that have been reported with sarilumab treatment are transient and/or reversible elevations in liver enzyme levels that appear to be dose dependent and rare occurrences of neutropenia and thrombocytopenia. Additional adverse effects, such as serious infections (e.g., TB, bacterial or fungal infections) and bowel perforation, have been reported, but only with long-term use of sarilumab.

Considerations in Pregnancy

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

Considerations in Children

The only data on sarilumab use in children are from ongoing trials evaluating the drug's safety in children with juvenile idiopathic arthritis. There are no systematic observational or randomized controlled trial data on the efficacy of sarilumab for the treatment of pediatric COVID-19 or MIS-C.

Drug Availability

The IV formulation of sarilumab is not approved by the FDA, but in a clinical trial, a single SQ dose (using the prefilled syringe, not the prefilled pen) of sarilumab 400 mg was reconstituted in 100 cc 0.9% NaCl and given as an IV infusion over a 1-hour period.

Anti-Interleukin-6 Monoclonal Antibody

Siltuximab

Siltuximab is a recombinant human-mouse chimeric mAb that binds IL-6 and is approved by the FDA for use in patients with multicentric Castleman 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.

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Clinical Data for COVID-19

There are limited data on the efficacy of siltuximab in patients with COVID-19.[23] 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 clinical trials that are evaluating the use of siltuximab for the treatment of 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 siltuximab-associated risk for major birth defects or miscarriage. mAbs are transported across the placenta as pregnancy progresses (with the greatest transfer occurring during the third trimester), and this may affect immune responses in the exposed fetus.

Considerations in Children

The safety and efficacy of siltuximab have not been established in pediatric patients.

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Table 4e. Interleukin-6 Inhibitors: Selected Clinical Data

Last Updated May 31, 2022

The clinical trials described in this table do not represent all the trials that the Panel reviewed while developing the recommendations for IL-6 inhibitors. The studies summarized below are those that have had the greatest impact on the Panel's recommendations.

This table may include data from preprints or articles that have not been peer reviewed. This table will be updated as new information becomes available.

Methods	Results	Limitations and Interpretation
RECOVERY: Open-Label RCT of Tocilizumab and Usual Care in Hospitalized Adults With COVID-19 in the United Kingdom[1]		

Key Inclusion Criteria:
• Evidence of COVID-19 progression ≤21 days after initial randomization to an intervention within the RECOVERY protocol, defined as:
  • SpO_2 <92% on room air or receipt of supplemental oxygen; *and*
  • CRP ≥75 mg/L
Key Exclusion Criterion:
• Non-SARS-CoV-2 infection
Interventions:
• Single weight-based dose of tocilizumab (maximum 800 mg) and possible second dose (n = 2,022)
• Usual care (n = 2,094)
Primary Endpoint:
• 28-day all-cause mortality
Key Secondary Endpoints:
• Time to discharge from hospital, alive, within 28 days
• Among those not on MV at enrollment, death or receipt of MV within 28 days
	Participant Characteristics:
	• Mean age 64 years; 67% men; 76% White
	• 95% with PCR-confirmed SARS-CoV-2 infection
	• At baseline:
	  • 45% on conventional oxygen
	  • 41% on HFNC oxygen or NIV
	  • 14% on MV
	  • 82% on corticosteroids
	Primary Outcomes:
	• 28-day all-cause mortality: 31% in tocilizumab arm vs. 35% in usual care arm (rate ratio 0.85; 95% CI, 0.76–0.94; $P = 0.003$)
	• 28-day all-cause mortality among those who required MV at baseline: 49% in tocilizumab arm vs. 51% in usual care arm (risk ratio 0.93; 95% CI, 0.74–1.18)
	Secondary Outcomes:
	• Proportion discharged alive from hospital within 28 days: 57% in tocilizumab arm vs. 50% in usual care arm (rate ratio 1.22; 95% CI, 1.12–1.33; $P < 0.0001$)
	• Median time to discharge: 19 days in tocilizumab arm vs. 28 days in usual care arm
	• Proportion not on MV at baseline who died or required MV within 28 days: 35% in tocilizumab arm vs. 42% in usual care arm (rate ratio 0.84; 95% CI, 0.77–0.92; $P < 0.0001$)
		Key Limitations:
		• Arbitrary CRP ≥75 mg/L cutoff for enrollment
		• Difficult to define exact subset of patients in RECOVERY cohort who were subsequently selected for secondary randomization/tocilizumab trial
		Interpretation:
		• Among hospitalized COVID-19 patients with hypoxemia and elevated CRP, tocilizumab was associated with reduced all-cause mortality and shorter time to discharge alive.

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Methods	Results	Limitations and Interpretation
REMAP-CAP: Open-Label, Adaptive-Platform RCT of Tocilizumab and Sarilumab in Adults With COVID-19 in 21 Countries in Europe and North America[2,3]		

Key Inclusion Criteria:
• ICU admission
• Suspected or laboratory-confirmed COVID-19
• Receipt of MV, NIV, or cardiovascular support
Key Exclusion Criteria:
• >24 hours after ICU admission
• Presumption of imminent death
• Immunosuppression
• ALT >5 times ULN
Interventions:
• SOC plus 1 of the following (drug selection based on provider preference, availability, or adaptive probability):
  • Single dose tocilizumab 8 mg/kg IV and possible second dose in 12–24 hours (n = 952)
  • Single dose sarilumab 400 mg IV (n = 485)
• SOC alone (n = 406)
Primary Endpoint:
• Composite of in-hospital mortality and organ support-free days to Day 21 (ordinal scale)
Key Secondary Endpoint:
• In-hospital survival
	Participant Characteristics:
	• Mean age 60 years; 69% men; 75% White
	• 86% PCR-confirmed SARS-CoV-2 infection
	• Median 14 hours from ICU admission to enrollment
	• At baseline:
	  • 68% on HFNC oxygen or NIV
	  • 32% on MV
	  • On corticosteroids: 67% in SOC arm, 82% in tocilizumab arm, 89% in sarilumab arm
	Primary Outcomes
	Tocilizumab vs. SOC:
	• Median organ support-free days: 7 in tocilizumab arm vs. 0 in SOC arm
	• Improved composite outcome, by ordinal scale: median aOR 1.46 (95% CrI, 1.13–1.87)
	  • Highest CRP tercile: aOR 1.87 (95% CrI, 1.35–2.59)
	• Outcomes consistent across subgroups according to oxygen requirement at baseline
	Sarilumab vs. SOC:
	• Median organ support-free days: 9 in sarilumab arm vs. 0 in SOC arm
	• Improved composite outcome, by ordinal scale: median aOR 1.50 (95% CrI, 1.13–2.00)
	  • Highest CRP tercile: aOR 1.85 (95% CrI, 1.24–2.69)
	• Outcomes consistent across subgroups according to oxygen requirements at study entry
	Secondary Outcomes
	Tocilizumab vs. SOC:
	• In-hospital survival: 66% in tocilizumab arm vs. 63% in SOC arm (aOR 1.42; 95% CrI, 1.05–1.93)
	Sarilumab vs. SOC:
	• In-hospital survival: 67% in sarilumab arm vs. 63% in SOC arm (aOR 1.51; 95% CrI, 1.06–2.20)
		Key Limitation:
		• The SOC arm closed in November 2020, after which patients were randomized to active arms only; enrollment in the tocilizumab and sarilumab arms was partially nonconcurrent with the SOC arm, and although comparisons to the SOC arm were adjusted for time period, there is a possibility of bias.
		Interpretation:
		• Among patients with respiratory failure who were within 24 hours of ICU admission, the tocilizumab and sarilumab arms had higher rates of in-hospital survival and shorter durations of organ support than the SOC arm.
		• These results were reported in a preprint and are consistent with those for a smaller cohort previously published in a peer-reviewed article.
		• The treatment effect appeared to be strongest in the highest CRP tercile.
		• Tocilizumab and sarilumab were similarly effective, with a 99% probability of noninferiority of sarilumab.

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Methods	Results	Limitations and Interpretation
COVACTA: Double-Blind RCT of Tocilizumab in Hospitalized Adults With COVID-19 in 9 Countries in Europe and North America[4]		
Key Inclusion Criteria: • PCR-confirmed SARS-CoV-2 infection • Hypoxemia • Bilateral chest infiltrates **Key Exclusion Criteria:** • Presumption of imminent death • Presence of active non-SARS-CoV-2 infection **Interventions:** • Single dose of tocilizumab 8 mg/kg and possible second dose, plus SOC (n = 294) • Placebo plus SOC (n = 144) **Primary Endpoint:** • Day 28 clinical status (ordinal score) **Key Secondary Endpoints:** • Time to discharge • ICU LOS • Day 28 mortality	**Participant Characteristics:** • Mean age 61 years; 70% men; 58% White • 30% on HFNC oxygen or NIV • 38% on MV • 25% with multiorgan failure • Received corticosteroids at entry or during follow-up: 36% in tocilizumab arm, 55% in placebo arm **Primary Outcome:** • Day 28 clinical status: no significant difference between arms (P = 0.31) **Secondary Outcomes:** • Median time to discharge: 20 days in tocilizumab arm vs. 28 days in placebo arm (HR 1.35; 95% CI, 1.02–1.79) • Median ICU LOS: 9.8 days in tocilizumab arm vs. 15.5 days in placebo arm (difference 5.8 days, 95% CI, –15.0 to 2.9) • Day 28 mortality: 20% in tocilizumab arm vs. 19% in placebo arm (P = 0.94)	**Key Limitations:** • Modest power to detect differences in Day 28 clinical status • More patients in placebo arm than tocilizumab arm received corticosteroids. **Interpretation:** • There was no difference in Day 28 clinical status or survival between the tocilizumab and placebo recipients. • The median time to discharge was significantly shorter in the tocilizumab arm than in the placebo arm. • Although the result was not statistically significant, the tocilizumab arm had a shorter ICU LOS than the placebo arm.

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Methods	Results	Limitations and Interpretation
EMPACTA: Double-Blind RCT of Tocilizumab in Hospitalized Adults With COVID-19 in 6 Countries in North America, South America, and Africa[5]		

Key Inclusion Criteria:
• PCR-confirmed SARS-CoV-2 infection
• COVID-19 pneumonia
Key Exclusion Criteria:
• Presumption of imminent death
• Receiving NIV or MV
Interventions:
• Single dose of tocilizumab 8 mg/kg plus SOC, possible second dose (n = 249)
• Placebo plus SOC (n = 128)
Primary Endpoint:
• Progression to MV, ECMO, or death by Day 28
Key Secondary Endpoints:
• Time to hospital discharge or readiness for discharge (ordinal score)
• All-cause mortality by Day 28
	Participant Characteristics:
	• Mean age 56 years; 59% men; 56% Hispanic/Latinx, 15% Black/African American, 13% American Indian/Alaska Native
	• 84% with elevated CRP
	• Concomitant medications:
	  • Corticosteroids: 80% in tocilizumab arm, 88% in placebo arm
	  • RDV: 53% in tocilizumab arm, 59% in placebo arm
	Primary Outcome:
	• Proportion who progressed to MV, ECMO, or death by Day 28: 12% in tocilizumab arm vs. 19% in placebo arm (HR 0.56; 95% CI, 0.33–0.97; $P = 0.04$)
	Secondary Outcomes:
	• Median time to hospital discharge or readiness for discharge: 6.0 days in tocilizumab arm vs. 7.5 days in placebo arm (HR 1.16; 95% CI, 0.91–1.48)
	• All-cause mortality by Day 28: 10.4% in tocilizumab arm vs. 8.6% in placebo arm (95% CI, –5.2 to 7.8)
		Key Limitation:
		• Moderate sample size
		Interpretation:
		• In patients with COVID-19 pneumonia, tocilizumab reduced the likelihood of progression to MV, ECMO, or death by Day 28 but did not reduce 28-day all-cause mortality.

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Methods	Results	Limitations and Interpretation
BACC Bay: Double-Blind RCT of Tocilizumab in Hospitalized Adults With COVID-19 in the United States[6]		

Key Inclusion Criteria:
• Laboratory-confirmed SARS-CoV-2 infection
• ≥2 of the following conditions:
  • Fever >38°C
  • Pulmonary infiltrates
  • Need for supplemental oxygen
• ≥1 of the following laboratory criteria:
  • CRP ≥50 mg/L
  • D-dimer >1,000 ng/mL
  • LDH ≥250 U/L
  • Ferritin >500 ng/mL
Key Exclusion Criteria:
• Receipt of supplemental oxygen at rate >10 L/min
• Recent use of biologic agents or small-molecule immunosuppressive therapy
• Receipt of immunosuppressive therapy that increased risk for infection
Interventions:
• Tocilizumab 8 mg/kg plus usual care (n = 161)
• Placebo plus usual care (n = 81)
Primary Endpoint:
• Receipt of MV or death, according to a time to event analysis; data censored at Day 28
Key Secondary Endpoints:
• Clinical worsening by Day 28 (ordinal score)
• Discontinuation of supplemental oxygen among patients receiving it at baseline
	Participant Characteristics:
	• Median age 60 years; 58% men; 45% Hispanic/Latinx, 43% White
	• 50% with BMI ≥30; 49% with HTN; 31% with DM
	• 80% receiving oxygen ≤6 L/min; 4% receiving HFNC oxygen; 16% receiving no supplemental oxygen
	• Concomitant medications:
	  • Corticosteroids: 11% in tocilizumab arm, 6% in placebo arm
	  • RDV: 33% in tocilizumab arm, 29% in placebo arm
	Primary Outcome:
	• Day 28 MV or death: 11% in tocilizumab arm vs. 12% in placebo arm (HR 0.83; 95% CI, 0.38–1.81; $P = 0.64$)
	Secondary Outcomes:
	• Proportion with clinical worsening of disease by Day 28: 19% in tocilizumab arm vs. 17% in placebo arm (HR 1.11; 95% CI, 0.59–2.10; $P = 0.73$)
	• Median days to discontinuation of oxygen: 5.0 in tocilizumab arm vs. 4.9 in placebo arm ($P = 0.69$)
		Key Limitations:
		• Wide confidence intervals due to small sample size and low event rates
		• Few patients received RDV or corticosteroids
		Interpretation:
		• There was no benefit of tocilizumab in preventing MV or death, reducing the risk of clinical worsening, or reducing the time to discontinuation of oxygen. This could be due to the low rate of concomitant corticosteroid use among the study participants.

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Methods	Results	Limitations and Interpretation
Double-Blind, RCT of Sarilumab in Hospitalized Adults With Severe or Critical COVID-19 in 11 Countries in Europe, North America, South America, and Asia[7]		

Key Inclusion Criteria:
• COVID-19 pneumonia
• Requirement for supplemental oxygen or intensive care
Key Exclusion Criteria:
• Low probability of surviving or remaining at study site
• Dysfunction of ≥2 organ systems and need for ECMO or renal replacement therapy
Interventions:
• Sarilumab 400 mg IV (n = 173)
• Sarilumab 200 mg IV (n = 159)
• Placebo (n = 84)
Primary Endpoint:
• Time to clinical improvement of ≥2 points on a 7-point scale
Key Secondary Endpoint:
• Survival at Day 29
	Participant Characteristics:
	• Median age 59 years; 63% men; 77% White, 36% Hispanic/Latinx
	• 39% on HFNC oxygen, MV, or NIV
	• 42% with BMI ≥30; 43% with HTN; 26% with type 2 DM
	• 20% received systemic corticosteroids before receiving intervention; 63% received ≥1 dose of corticosteroids during the study
	Primary Outcomes:
	• Median time to clinical improvement: 10 days in each sarilumab arm, 12 days in placebo arm
	  • Sarilumab 200 mg arm vs. placebo arm: HR 1.03; 95% CI, 0.75–1.40; $P = 0.96$
	  • Sarilumab 400 mg arm vs. placebo arm: HR 1.14; 95% CI, 0.84–1.54; $P = 0.34$
	Secondary Outcome:
	• Survival at Day 29: 92% in placebo arm; 90% in sarilumab 200 mg arm ($P = 0.63$ vs. placebo); 92% in sarilumab 400 mg arm ($P = 0.85$ vs. placebo)
		Key Limitation:
		• Moderate sample size
		Interpretation:
		• Sarilumab showed no mortality benefit or reduction in time to clinical improvement in hospitalized adults with COVID-19.

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Methods	Results	Limitations and Interpretation
REMDACTA: Double-Blind RCT of Tocilizumab and Remdesivir in Hospitalized Patients With Severe COVID-19 Pneumonia in Brazil, Russia, Spain, and the United States[8]		

Key Inclusion Criteria:
• Aged ≥12 years
• PCR-confirmed SARS-CoV-2 infection
• Hospitalized with pneumonia confirmed by CXR or CT and requiring supplemental oxygen >6 L/min
Key Exclusion Criteria:
• eGFR <30 mL/min
• ALT or AST >5 times ULN
• Presence of non-SARS-CoV-2 infection
• Treatment with antivirals, CP, CQ, HCQ, JAK inhibitors
Interventions:
• Up to 10 days RDV plus:
  • Tocilizumab 8 mg/kg IV, with second dose within 8–24 hours if indicated (n = 434)
  • Placebo (n = 215)
Primary Endpoint:
• Time to discharge or ready for discharge through Day 28
Key Secondary Endpoints:
• Time to MV or death through Day 28
• Day 14 clinical status (ordinal score)
• Time to death through Day 28
	Participant Characteristics:
	• Mean age 59 years; 40% in tocilizumab arm and 34% in placebo arm aged ≥65 years; 63% men; 67% White
	• Respiratory support:
	  • NIV or HFNC oxygen: 78% in tocilizumab arm, 83% in placebo arm
	  • MV or ECMO: 15% in tocilizumab arm, 11% in placebo arm
	• Corticosteroid use:
	  • At baseline: 83% in tocilizumab arm, 86% in placebo arm
	  • During trial: 88% in each arm
	Primary Outcome:
	• Time to discharge or ready for discharge through Day 28: 14 days in each arm (HR 0.97; 95% CI, 0.78–1.19; *P* = 0.74)
	Secondary Outcomes:
	• No difference between arms:
	  • Proportion who required MV or died by Day 28: 29% in each arm; time to death not evaluable (HR 0.98; 95% CI, 0.72–1.34; *P* = 0.90)
	  • Mean ordinal score for Day 14 clinical status: 2.8 in tocilizumab arm vs. 2.9 in placebo arm (*P* = 0.72)
	  • Death by Day 28: 18% in tocilizumab arm vs. 20% in placebo arm; time to death not evaluable (HR 0.95; 95% CI, 0.65–1.39; *P* = 0.79)
		Key Limitations:
		• During the trial, primary outcome changed from clinical status on Day 28 to time to discharge or ready for discharge through Day 28
		• Imbalances in patient characteristics at baseline between arms
		• Possible underrepresentation of patients with rapidly progressive disease
		Interpretation:
		• Compared with placebo plus RDV, tocilizumab plus RDV did not shorten the time to discharge or ready for discharge in patients with severe COVID-19 pneumonia.
		• There was no difference in mortality between the arms.

Key: ALT = alanine transaminase; AST = aspartate transaminase; BMI = body mass index; CP = convalescent plasma; CQ = chloroquine; CRP = C-reactive protein; CT = computed tomography; CXR = chest X-ray; DM = diabetes mellitus; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; HCQ = hydroxychloroquine; HFNC = high-flow nasal cannula; HTN = hypertension; ICU = intensive care unit; IL = interleukin; IV = intravenous; JAK = Janus kinase; LDH = lactate dehydrogenase; LOS = length of stay; MV = mechanical ventilation; NIV = noninvasive ventilation; the Panel = the COVID-19 Treatment Guidelines Panel; PCR = polymerase chain reaction; RCT = randomized controlled trial; RDV = remdesivir; SOC = standard of care; SpO_2 = oxygen saturation; ULN = upper limit of normal

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

Last Updated: December 16, 2021

Janus Kinase Inhibitors

Janus kinase (JAK) inhibitors interfere with phosphorylation of signal transducer and activator of transcription (STAT) proteins[1,2] that are involved in vital cellular functions, including signaling, growth, and survival. These 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).[3]

Immunosuppression induced by JAK inhibitors 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 SARS-CoV-2 from entering and infecting susceptible cells.[4]

Recommendations

- See Therapeutic Management of Hospitalized Adults With COVID-19 for the COVID-19 Treatment Guidelines Panel's (the Panel) recommendations on the use of baricitinib and tofacitinib for certain hospitalized patients who require oxygen supplementation.
- The Panel **recommends against** the use of **JAK inhibitors other than baricitinib or tofacitinib** for the treatment of COVID-19, except in a clinical trial **(AIII)**.

Rationale

The Panel's recommendations are based on data from the ACTT-2,[5] COV-BARRIER,[6] and STOP-COVID[7] clinical trials. The ACTT-2 trial demonstrated that baricitinib improved time to recovery when given in combination with remdesivir to hospitalized patients with COVID-19 who require supplemental oxygen but not mechanical ventilation. However, a key limitation of the ACTT-2 trial is that corticosteroids were not used as the standard of care; thus, it was not possible to evaluate the effect of baricitinib when given in addition to corticosteroids.

The COV-BARRIER trial enrolled patients with COVID-19 pneumonia and at least 1 elevated inflammatory marker at enrollment who were not on mechanical ventilation. This trial reported an additional survival benefit of baricitinib when added to the standard of care of corticosteroids (with or without remdesivir). If baricitinib is not available, tofacitinib may be an alternative because it has demonstrated clinical benefit in the STOP-COVID trial.

The clinical trial data on the use of baricitinib and tofacitinib in patients with COVID-19 is summarized below, and all related treatment recommendations are reviewed in Therapeutic Management of Hospitalized Adults With COVID-19.

Monitoring, Adverse Effects, and Drug-Drug Interactions

Most of the data on adverse effects of JAK inhibitors were reported based on chronic use of the agents for the treatment of autoimmune diseases. Adverse effects include infections (typically respiratory and urinary tract infections) and the reactivation of herpes viruses; myelosuppression; transaminase elevations; and, rarely, gastrointestinal perforation. The Food and Drug Administration (FDA) review of a large, randomized, safety clinical trial comparing tofacitinib to antitumor necrosis factor inhibitors in people with rheumatoid arthritis found that tofacitinib was associated with additional serious adverse

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events, including heart attack or stroke, cancer, blood clots, and death.[8] The FDA is therefore requiring new and updated warnings for drugs in the JAK inhibitor class, including tofacitinib and baricitinib. Data from randomized trials evaluating the safety of short-term use of JAK inhibitors in patients with COVID-19 are limited. The data to date have not revealed significant safety signals, including thrombosis; however, these trials may be underpowered for detecting rare adverse events.[5-7]

A 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.

Tofacitinib is a cytochrome P 450 (CYP) 3A4 substrate. Dose modifications are required when the drug is administered with strong CYP3A4 inhibitors or when used with a moderate CYP3A4 inhibitor that is coadministered with a strong CYP2C19 inhibitor. Coadministration with a strong CYP3A4 inducer **is not recommended**.

The ACTT-2 and COV-BARRIER trials evaluated oral baricitinib 4 mg once daily, which is twice the standard baricitinib dose (2 mg once daily) for FDA-approved indications.[5,6] In patients with severe hepatic impairment, baricitinib should only be used if the potential benefit outweighs the potential risk.[9] Baricitinib has not been evaluated in clinical studies for FDA-approved indications in patients with an estimated glomerular filtration rate (eGFR) ≤30 mL/min. When baricitinib is used for the treatment of COVID-19 in adults with renal insufficiency, the Panel recommends reducing the dose of baricitinib from 4 mg to 2 mg daily for adults with an eGFR ≥30 to <60 mL/min and to 1 mg daily for those with an eGFR of 15 to <30 mL/min. Baricitinib **is not recommended** for patients with an eGFR <15 mL/min.[9] 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.[10,11]

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.[12] Decisions regarding the administration of JAK inhibitors must include shared decision-making between the pregnant individual and their health care provider, 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. Pregnancy registries provide some outcome data on tofacitinib use 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 population.[13-15]

Considerations in Children

An FDA Emergency Use Authorization (EUA) has been issued for the use of baricitinib in hospitalized adults and children aged ≥2 years with COVID-19 who require supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).[9] The safety and efficacy of baricitinib have not been evaluated in pediatric patients with COVID-19. As noted above, tofacitinib was shown to decrease the risk of respiratory failure and death in adults with COVID-19 in the STOP-COVID trial.[7] Tofacitinib is FDA approved for a pediatric indication; however, the safety and efficacy of tofacitinib have not been evaluated in pediatric patients with COVID-19. Thus, there is insufficient evidence to recommend either for or against the use of baricitinib in combination with corticosteroids and/or remdesivir for the treatment of COVID-19 in hospitalized children.

Baricitinib

Baricitinib is an oral JAK inhibitor that is selective for JAK1 and JAK2 and is FDA approved for the

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treatment of rheumatoid arthritis.[10] Baricitinib can modulate downstream inflammatory responses via JAK1/JAK2 inhibition and has exhibited dose-dependent inhibition of IL-6-induced STAT3 phosphorylation.[16] Baricitinib has postulated antiviral effects by blocking SARS-CoV-2 from entering and infecting lung cells.[17] Baricitinib reduced inflammation and lung pathology in macaques infected with SARS-CoV-2, but an antiviral effect was not confirmed.[18]

Clinical Data for COVID-19

In the ACTT-2 trial, 1,033 patients hospitalized with COVID-19 were randomized 1:1 to receive baricitinib 4 mg daily for 14 days (or until hospital discharge) or placebo, both given in combination with remdesivir. The primary endpoint was time to recovery as measured on an 8-category ordinal scale. Recovery time was shorter in the baricitinib arm (7 days) than in the placebo arm (8 days) (rate ratio for recovery 1.16; 95% CI, 1.01–1.32; $P = 0.03$). Mortality by 28 days was lower in the baricitinib arm than in the placebo arm, but the difference was not statistically significant. A key limitation of the study is that corticosteroids were not used as background standard care for patients with severe or critical COVID-19 pneumonia.[5]

In the COV-BARRIER trial, 1,525 hospitalized patients with COVID-19 pneumonia and an elevation in 1 or more inflammatory markers were randomized 1:1 to receive baricitinib 4 mg orally or placebo for up to 14 days (or until hospital discharge). Patients on mechanical ventilation were excluded from study enrollment. Overall, 79% of patients received corticosteroids and 19% received remdesivir. The primary endpoint was the proportion of patients who progressed to high-flow oxygen, noninvasive ventilation, mechanical ventilation, or death by Day 28. Progression to the primary endpoint occurred among 27.8% of patients in the baricitinib arm versus 30.5% in the placebo arm (OR 0.85; 95% CI, 0.67–1.08; $P = 0.18$). All-cause mortality within 28 days, which was a key secondary endpoint, was 8.1% in the baricitinib arm and 13.1% in the placebo arm, resulting in a 38.2% reduction in mortality associated with baricitinib (HR 0.57; 95% CI, 0.41–0.78). The mortality difference was most pronounced in the subgroup of patients receiving high-flow oxygen or noninvasive ventilation at baseline (17.5% for baricitinib recipients vs. 29.4% for placebo recipients; HR 0.52; 95% CI, 0.33–0.80). However, subgroup analyses did not identify a statistically significant benefit of baricitinib versus placebo among patients receiving low-flow oxygen at baseline. The occurrence of adverse events, serious adverse events, serious infections, and venous thromboembolic events was comparable in the baricitinib and placebo arms.[6]

The COV-BARRIER trial added a critically ill cohort to the original study. In this cohort, participants on mechanical ventilation or ECMO at baseline (n = 101) were randomly assigned to baricitinib 4 mg (n = 51) or placebo (n = 50) for up to 14 days in combination with the standard of care. At baseline, 86% of participants were receiving corticosteroids and 2% were receiving remdesivir. Baricitinib significantly reduced the prespecified endpoint of 28-day all-cause mortality when compared with placebo (39.2% vs. 58.0%; HR 0.54; 95% CI, 0.31–0.96; $P = 0.03$). Significant reductions were also reported with baricitinib versus placebo in 60-day mortality (45% vs. 62%; $P = 0.027$) and hospital days (23.7 vs. 26.1 days; $P = 0.05$). The implications of these findings are limited due to the very small sample size of this addendum trial population.[19]

The collective data from these studies have informed the Panel's recommendations on the use of baricitinib in hospitalized patients with COVID-19. The specific recommendations and additional information on the rationale can be found in Therapeutic Management of Hospitalized Adults With COVID-19.

Clinical Trials

Please see ClinicalTrials.gov for the latest information on studies of baricitinib for the treatment of COVID-19.

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Drug Availability

Baricitinib is approved by the FDA for the treatment of rheumatoid arthritis. On November 19, 2020, the FDA issued an initial EUA for the use of baricitinib in combination with remdesivir for the treatment of COVID-19 in certain hospitalized children and adults who require supplemental oxygen, mechanical ventilation, or ECMO. The EUA was revised on July 28, 2021, to remove the requirement that baricitinib be used only in combination with remdesivir for the treatment of COVID-19.[9]

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 glycoprotein 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.[20] Tofacitinib is also FDA approved for the treatment of psoriatic arthritis, juvenile idiopathic arthritis, and ulcerative colitis.[21]

Clinical Data for COVID-19

The double-blind STOP-COVID trial randomized 289 hospitalized patients with COVID-19 in Brazil to receive tofacitinib 10 mg or placebo orally twice daily for up to 14 days (or until hospital discharge). Patients who were on mechanical ventilation or who had an immunocompromising condition were excluded from the trial. The background standard of care included corticosteroids (79.2% of patients were receiving corticosteroids at randomization and overall, 89.3% received corticosteroids during the study) but not remdesivir. The primary outcome of death or respiratory failure through Day 28 occurred in 18.1% of patients in the tofacitinib arm and 29.0% in the placebo arm (risk ratio 0.63; 95% CI, 0.41–0.97). All-cause mortality within 28 days was 2.8% in the tofacitinib arm and 5.5% in the placebo arm (risk ratio 0.49; 95% CI, 0.15–1.63). Serious adverse events occurred in 14.2% of the patients in the tofacitinib arm and 12.0% in the placebo arm. Limitations of the trial include the small sample size.[7]

Clinical Trials

Please see ClinicalTrials.gov for the latest information on studies of tofacitinib for the treatment of 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.[22] Like baricitinib, it can modulate downstream inflammatory responses via JAK1/JAK2 inhibition and has exhibited dose-dependent inhibition of IL-6-induced STAT3 phosphorylation.[16] Ruxolitinib also has postulated antiviral effects by blocking SARS-CoV-2 from entering and infecting lung cells.[17]

Clinical Data for COVID-19

A small, single-blind, Phase 2 randomized controlled 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 standard of care. Treatment with ruxolitinib was associated with a nonsignificant reduction in the median time to clinical improvement (12 days for ruxolitinib recipients vs. 15 days for placebo recipients; $P = 0.15$), defined as a 2-point improvement on a 7-category ordinal scale or as hospital discharge. There was no difference between the arms in the median time to discharge (17 days for ruxolitinib arm vs. 16 days for placebo arm; $P = 0.94$). Limitations of this study include the small sample size.[23] A Phase 3 trial of ruxolitinib in patients with COVID-19-associated acute respiratory distress syndrome is currently in progress (ClinicalTrials.gov Identifier NCT04377620).

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Clinical Trials

Please see ClinicalTrials.gov for the latest information on studies of ruxolitinib for the treatment of 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 it has less off-target activity for other kinases.[24] 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 prospective case series of 19 patients with severe COVID-19.[25] 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 see ClinicalTrials.gov for the latest information on studies of acalabrutinib for the treatment of COVID-19.

Ibrutinib

Ibrutinib is a first-generation BTK inhibitor that is FDA approved to treat various B-cell malignancies[26] and to prevent chronic graft-versus-host disease in stem cell transplant recipients.[27] 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.[28]

Clinical Data for COVID-19

Data regarding ibrutinib are limited to those from an uncontrolled, retrospective case series of 6 patients with COVID-19 who were receiving the drug for a condition other than COVID-19.[28] 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 see ClinicalTrials.gov for the latest information on studies of ibrutinib for the treatment of COVID-19.

Zanubrutinib

Zanubrutinib is a second-generation, oral BTK inhibitor that is FDA approved to treat mantle cell lymphoma.[29] 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.[30] Zanubrutinib is proposed to benefit patients with COVID-19 by modulating signaling that promotes inflammation.

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Clinical Data for COVID-19

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

Clinical Trials

Please see ClinicalTrials.gov for the latest information on studies of zanubrutinib for the treatment of 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.[26,31] 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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Table 4f. Characteristics of Immunomodulators

Last Updated: May 31, 2022

- 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.
- For dose modifications for patients with organ failure or those who require extracorporeal devices, please refer to product labels or EUAs, 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 certain 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 the Panel's recommendations on using the drugs listed in this table, please refer to the drug-specific sections of the Guidelines, to Therapeutic Management of Nonhospitalized Adults With COVID-19, and Therapeutic Management of Hospitalized Adults With COVID-19.

Drug Name	Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Colchicine *Not approved by the FDA and not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*					
Colchicine	**Dose for COVID-19 in COLCORONA Trial:** • Colchicine 0.5 mg twice daily for 3 days and then once daily for 27 days[1] **Dose for COVID-19 in COLCOVID Trial:** • Colchicine 1.5 mg PO followed by 0.5 mg PO within 2 hours of initial dose and then twice daily for 14 days or until hospital discharge, whichever comes first[2]	• Diarrhea • Nausea • Vomiting • Cramping • Abdominal pain • Bloating • Loss of appetite • Neuro-myotoxicity (rare)[3] • Blood dyscrasias (rare)	• CBC • Renal function • Hepatic function	• P-gp and CYP3A4 substrate • The risk of myopathy may be increased with the concomitant use of certain HMG-CoA reductase inhibitors (e.g., atorvastatin, lovastatin, simvastatin) due to potential competitive interactions mediated by P-gp and CYP3A4 pathways. • Fatal colchicine toxicity has been reported in individuals with renal or hepatic impairment who used colchicine in conjunction with P-gp inhibitors or strong CYP3A4 inhibitors.	• Use of colchicine **should be avoided** in patients with severe renal insufficiency; patients with moderate renal insufficiency who receive the drug should be monitored for AEs. • A list of clinical trials is available: Colchicine **Availability:** • In the COLCORONA and COLCOVID trials, 0.5 mg colchicine tablets were used for dosing; in the United States, colchicine is available as 0.6 mg tablets.

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Drug Name	Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Corticosteroids (Inhaled) *Not approved by the FDA and not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*					
Budesonide (Inhaled)	**Dose for COVID-19 in Clinical Trials:** • Budesonide 800 mcg oral inhalation twice daily until symptom resolution or for up to 14 days[4,5]	• Secondary infections • Oral thrush • Systemic AEs (less common)	• Signs of AEs involving the oral mucosa or throat, including thrush • Signs of systemic corticosteroid effects (e.g., adrenal suppression)	• CYP3A4 substrate • **Do not use** with strong CYP3A4 inhibitors.	• A list of clinical trials is available: Inhaled Budesonide
Ciclesonide (Inhaled)	**Dose for COVID-19 in Clinical Trials:** • Ciclesonide 160 mcg: 2 MDI inhalations twice daily for 30 days[6]	• Secondary infections • Oral thrush • Systemic AEs (less common)	• Signs of AEs involving the oral mucosa or throat, including thrush • Signs of systemic corticosteroid effects (e.g., adrenal suppression)	• CYP3A4 substrate • Effect of strong CYP3A4 inhibitors on ciclesonide exposure is not expected to be as significant as that on budesonide.	• A list of clinical trials is available: Ciclesonide

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Drug Name	Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Corticosteroids (Systemic) *Recommended by the Panel for the treatment of COVID-19 in certain hospitalized patients.*					

Dexamethasone (Systemic)	**Dose for COVID-19:**
	• DEX 6 mg IV or PO once daily for up to 10 days or until hospital discharge, whichever comes first[7]
		• Hyperglycemia
		• Secondary infections
		• Reactivation of latent infections (e.g., HBV, HSV, strongyloidiasis, TB)
		• Cases of disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with corticosteroids and tocilizumab.
		• Psychiatric disturbances
		• Avascular necrosis
		• Adrenal insufficiency
		• Increased BP
		• Peripheral edema
		• Myopathy (particularly if used with neuromuscular blocking agents)
			• Blood glucose
			• BP
			• Signs and symptoms of new infection
				• Moderate CYP3A4 inducer
				• CYP3A4 substrate
					• If DEX is not available, an alternative corticosteroid (e.g., prednisone, methylprednisolone, hydrocortisone) can be used.
					• The approximate total daily dose equivalencies for these glucocorticoids to DEX 6 mg (PO or IV) are:
					  • Prednisone 40 mg
					  • Methylprednisolone 32 mg
					  • Hydrocortisone 160 mg
					• A list of clinical trials is available: Dexamethasone

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Drug Name	Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Fluvoxamine *Not approved by the FDA and not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*					
Fluvoxamine	**Doses for COVID-19 in Clinical Trials:** • Various dosing regimens used, including: • Fluvoxamine 50 mg twice daily • Fluvoxamine 100 mg twice daily • Fluvoxamine 100 mg 3 times daily	• Nausea • Diarrhea • Dyspepsia • Asthenia • Insomnia • Somnolence • Sweating • Suicidal ideation (rare)	• Hepatic function • Drug interactions • Withdrawal symptoms during dose tapering	• CYP2D6 substrate • Fluvoxamine inhibits several CYP isoenzymes (CYP1A2, CYP2C9, CYP3A4, CYP2C19, CYP2D6) • Coadministration of tizanidine, thioridazine, alosetron, or pimozide with fluvoxamine is **contraindicated**.	• Fluvoxamine may enhance anticoagulant effects of antiplatelets and anticoagulants; consider additional monitoring when these drugs are used concomitantly with fluvoxamine. • The use of MAOIs concomitantly with fluvoxamine or within 14 days of treatment with fluvoxamine is **contraindicated**. • A list of clinical trials is available: Fluvoxamine
Interleukin-1 Inhibitors *Not approved by the FDA and not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*					
Anakinra	**FDA-Approved Dose for Rheumatoid Arthritis:** • Anakinra 100 mg SUBQ once daily **Doses for COVID-19 in Clinical Trials:** • Dose and duration vary by study. • Has also been used as IV infusion.	• Neutropenia (particularly when used concomitantly with other agents that can cause neutropenia) • Anaphylaxis and angioedema • Headache • Nausea • Diarrhea • Sinusitis • Arthralgia • Flu-like symptoms • Abdominal pain • Injection site reactions • Liver enzyme elevations	• CBC with differential • Liver enzymes • Renal function; reduce dose if CrCl <30 mL/min.	• Use with TNF-blocking agents **is not recommended** due to increased risk of infection. • **Avoid** concomitant administration of live vaccines.	• Anakinra for IV administration is not an approved formulation in the United States.[8] • A list of clinical trials is available: Anakinra

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Drug Name	Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Interleukin-1 Inhibitors, continued					
Canakinumab	**FDA-Approved Dose for Systemic Juvenile Idiopathic Arthritis:** • Canakinumab 4 mg/kg (maximum 300 mg) SUBQ every 4 weeks[9]	• HSR • Neutropenia • Nasopharyngitis • Diarrhea • Respiratory tract infections • Bronchitis • Gastroenteritis • Pharyngitis • Musculoskeletal pain • Vertigo • Abdominal pain • Injection site reactions • Liver enzyme elevations	• HSR • CBC with differential • Liver enzymes	• Binding of canakinumab to IL-1 may increase formation of CYP enzymes and alter metabolism of drugs that are CYP substrates. • Use with TNF-blocking agents **is not recommended** due to potential increased risk of infection. • **Avoid** concomitant administration of live vaccines.	• Canakinumab for IV administration is not an approved formulation in the United States.[9] • A list of clinical trials is available: Canakinumab

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Drug Name	Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Interleukin-6 Inhibitors					
Anti-Interleukin-6 Receptor Monoclonal Antibodies *Recommended by the Panel for the treatment of COVID-19 in certain nonhospitalized and hospitalized patients.*					
Sarilumab[10]	**Dose for COVID-19 in Clinical Trials:** • Single dose of sarilumab 400 mg IV[11]	• Neutropenia, thrombocytopenia • GI perforation • HSR • Increased liver enzymes • HBV reactivation • Infusion-related reaction	• HSR • Infusion reactions • Neutrophils • Platelets • Liver enzymes	• Elevated IL-6 may downregulate CYP enzymes; thus, use of sarilumab may lead to increased metabolism of drugs that are CYP substrates. • The effects of sarilumab on CYP enzymes may persist for weeks after the drug is stopped.	• Treatment with sarilumab may mask signs of acute inflammation or infection by suppressing fever and CRP levels. • A list of clinical trials is available: Sarilumab **Availability:** • The IV formulation of sarilumab is not approved by the FDA, but in a clinical trial, a single SUBQ dose (using the prefilled syringe, **not** the prefilled pen) of sarilumab 400 mg was reconstituted in 100 cc 0.9% NaCl and given as an IV infusion over 1 hour. • Sarilumab infusion should be used within 4 hours of preparation; it can be stored at room temperature until administered.

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Drug Name	Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Interleukin-6 Inhibitors, continued					
Anti-Interleukin-6 Receptor Monoclonal Antibodies, continued					
Tocilizumab[12]	**FDA EUA Doses for COVID-19 for Hospitalized Patients Aged ≥2 Years, Based on Body Weight:** • <30 kg: tocilizumab 12 mg/kg (maximum 800 mg) by IV infusion over 1 hour • ≥30 kg: tocilizumab 8 mg/kg (maximum 800 mg) by IV infusion over 1 hour • Per the EUA, if clinical signs or symptoms worsen or do not improve following the first infusion, 1 additional dose may be administered ≥8 hours after the first dose.	• Infusion-related reaction • HSR • GI perforation • Hepatotoxicity • Treatment-related changes on laboratory tests for neutrophils, platelets, lipids, and liver enzymes • HBV reactivation • Secondary infections • Cases of disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with tocilizumab and corticosteroids.	• HSR • Infusion reactions • Neutrophils • Platelets • Liver enzymes	• Inhibition of IL-6 may lead to increased metabolism of coadministered drugs that are CYP450 substrates. • The effects of tocilizumab on CYP enzymes may persist for weeks after the drug is stopped.	• The SUBQ formulation of tocilizumab **is not intended** for IV administration. • A list of clinical trials is available: Tocilizumab **Availability:** • IV tocilizumab, which has been approved for non-COVID-19 indications, is available commercially and through an FDA EUA for the treatment of COVID-19 in hospitalized adults and pediatric patients aged ≥2 years who are receiving systemic corticosteroids and require supplemental oxygen, NIV, MV, or ECMO. The EUA does not authorize the use of SUBQ administration of tocilizumab for the treatment of COVID-19.[13]

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Drug Name	Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Anti-Interleukin-6 Monoclonal Antibody *Not approved by the FDA and not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*					
Siltuximab	**FDA-Approved Dose for Multicentric Castleman Disease:** • Siltuximab 11 mg/kg by IV infusion over 1 hour every 3 weeks[14] **Dose for COVID-19:** • Dose and duration unknown	• Infusion-related reaction • HSR • GI perforation • Neutropenia • HTN • Dizziness • Rash • Pruritus • Hyperuricemia	• Neutrophils • HSR • Infusion reactions	• Elevated IL-6 may downregulate CYP enzymes; use of siltuximab may lead to increased metabolism of drugs that are CYP substrates. • The effects of siltuximab on CYP enzymes may persist for weeks after therapy is stopped.	• Treatment with siltuximab may mask signs of acute inflammation or infection by suppressing fever and CRP levels. • A list of clinical trials is available: Siltuximab

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Drug Name	Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Kinase Inhibitors					
Janus Kinase Inhibitors *Baricitinib and tofacitinib: Recommended by the Panel for the treatment of COVID-19 in certain hospitalized patients.* *Ruxolitinib: Not approved by the FDA and not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*					

Baricitinib[15]	**FDA-Approved Doses for COVID-19 for Adults Aged ≥18 Years, Based on eGFR:**[15]
	• ≥60 mL/min/1.73 m^2: baricitinib 4 mg PO once daily
	• 30 to <60 mL/min/1.73 m^2: baricitinib 2 mg PO once daily
	• 15 to <30 mL/min/1.73 m^2: baricitinib 1 mg PO once daily
	• eGFR <15 mL/min/1.73 m^2: **not recommended**
	FDA EUA Dose Authorized for Children Aged 9–17 Years:[16]
	• Same as adults
	EUA Doses Authorized for Children Aged 2 to <9 Years, Based on eGFR:[16]
	• ≥60 mL/min/1.73m^2: baricitinib 2 mg PO once daily
	• 30 to <60 mL/min/1.73m^2: baricitinib 1 mg PO once daily
	• <30 mL/min/1.73m^2: **not recommended**
	Duration of Therapy:
	• For up to 14 days or until hospital discharge
		• Lymphoma and other malignancies
		• Thrombosis
		• GI perforation
		• Treatment-related changes in lymphocytes, neutrophils, Hgb, liver enzymes
		• HSV reactivation
		• Herpes zoster
		• Serious cardiac-related events (e.g., MI, stroke)
			• CBC with differential
			• Renal function
			• Liver enzymes
			• New infections
				• Dose modification is recommended when administering concurrently with a strong OAT3 inhibitor.
				• **Avoid** concomitant administration of live vaccines.
					• See the FDA label[15] and EUA[16] for dosing guidance for patients with:
					  • ALC <200 cells/μL
					  • ANC <500 cells/μL
					• If increases in ALT or AST are observed and DILI is suspected, interrupt baricitinib treatment until the diagnosis of DILI is excluded.
					• Baricitinib tablets are to be taken orally or can be crushed, dispersed in water, and given via a gastrostomy tube.[15]
					• A list of clinical trials is available: Baricitinib
					Availability:
					• Baricitinib is approved by the FDA for the treatment of COVID-19 for adults aged ≥18 years and is available through an FDA EUA for children aged 2–17 years who require supplemental oxygen, NIV, MV, or ECMO.[16]

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Drug Name	Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Kinase Inhibitors, continued					
Janus Kinase Inhibitors, continued					
Ruxolitinib	**Dose for FDA-Approved Indications:** • Ruxolitinib 5 mg–20 mg PO twice daily **Dose for COVID-19 in Clinical Trials:** • Ruxolitinib 5 mg PO twice daily for 14 days[17]	• Thrombo-cytopenia • Anemia • Neutropenia • Liver enzyme elevations • Risk of infection • Dizziness • Headache • Diarrhea • CPK elevation • Herpes zoster	• CBC with differential • Liver enzymes • New infections	• Dose modification required when administered with strong CYP3A4 inhibitor. • **Avoid** use with fluconazole doses >200 mg.	• Dose modification may be required in patients with hepatic impairment, moderate or severe renal impairment, or thrombocytopenia. • A list of clinical trials is available: Ruxolitinib
Tofacitinib	**Dose for COVID-19 in Clinical Trials:** • Tofacitinib 10 mg PO twice daily for up to 14 days or until hospital discharge[18]	• Thrombotic events (e.g., PE, DVT, arterial thrombosis) • Anemia • Risk of infection • GI perforation • Diarrhea • Headache • Herpes zoster • Lipid elevations • Liver enzyme elevations • Lymphoma and other malignancies • Serious cardiac-related events (e.g., MI, stroke)	• CBC with differential • Liver enzymes • New infections	• Dose modifications required when administered with strong CYP3A4 inhibitors or when used with a moderate CYP3A4 inhibitor that is coadministered with a strong CYP2C19 inhibitor. • Coadministration with strong CYP3A4 inducers **is not recommended**. • **Avoid** concomitant administration of live vaccines.	• 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

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Drug Name	Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Non-SARS-CoV-2 Specific Immunoglobulin *Primarily used for the treatment of multisystem inflammatory syndrome in children (MIS-C). Currently under investigation in clinical trials.*					
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 • AEs may vary by formulation. • AEs may be increased with high dose or rapid infusion or in patients with underlying conditions.	• Transfusion-related reactions • Vital signs at baseline and during and after infusion • Renal function; discontinue treatment if function deteriorates.	• IVIG may interfere with immune response to certain vaccines.	• A list of clinical trials is available: Intravenous Immunoglobulin

Key: AE = adverse event; ALC = absolute lymphocyte count; ALT = alanine transaminase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BP = blood pressure; CBC = complete blood count; CPK = creatine phosphokinase; CrCl = creatinine clearance; CRP = C-reactive protein; CYP = cytochrome P450; DEX = dexamethasone; DILI = drug-induced liver injury; DVT = deep vein thrombosis; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; GI = gastrointestinal; HBV = hepatitis B; Hgb = hemoglobin; HSR = hypersensitivity reaction; HSV = herpes simplex virus; HTN = hypertension; IL = interleukin; IV = intravenous; IVIG = intravenous immunoglobulin; MAOI = monoamine oxidase inhibitor; MDI = metered dose inhaler; MI= myocardial infarction; MV = mechanical ventilation; NaCl = sodium chloride; NIV = noninvasive ventilation; OAT = organic anion transporter; the Panel = the COVID-19 Treatment Guidelines Panel; PE = pulmonary embolism; P-gp= P-glycoprotein; PO = orally; SUBQ = subcutaneous; TB = tuberculosis; TNF = tumor necrosis factor; TRALI = transfusion-related acute lung injury

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Antithrombotic Therapy in Patients with COVID-19

Last Updated: May 31, 2022

Summary Recommendations
Chronic Anticoagulant and Antiplatelet Therapy • The COVID-19 Treatment Guidelines Panel (the Panel) recommends that hospitalized patients with COVID-19 who are receiving anticoagulant or antiplatelet therapy for underlying medical conditions continue this treatment unless significant bleeding develops, or other contraindications are present **(AIII)**. **Screening and Evaluation for Venous Thromboembolism** • In patients with COVID-19 who have no signs or symptoms of venous thromboembolism (VTE), there is currently insufficient evidence to recommend either for or against routine VTE screening, regardless of the patient's coagulation markers. • For hospitalized patients with COVID-19 who experience rapid deterioration of pulmonary, cardiac, or neurological function or sudden, localized loss of peripheral perfusion, the Panel recommends evaluating the patients for thromboembolic disease **(AIII)**. **Anticoagulant Treatment for Thrombosis** • The Panel recommends that when diagnostic imaging is not possible, patients with COVID-19 who are highly suspected to have thromboembolic disease be managed with therapeutic anticoagulation **(AIII)**. • The Panel recommends that patients with COVID-19 who require extracorporeal membrane oxygenation or continuous renal replacement therapy or who have thrombosis related to catheters or extracorporeal filters be treated with antithrombotic therapy as per the standard institutional protocols for those without COVID-19 **(AIII)**. **Antithrombotic Therapy for Nonhospitalized Patients Without Evidence of Venous Thromboembolism** • In nonhospitalized patients with COVID-19, the Panel **recommends against** the use of anticoagulants and antiplatelet therapy (aspirin or P2Y12 inhibitors) for the prevention of VTE or arterial thrombosis unless the patient has other indications for the therapy or is participating in a clinical trial **(AIIa)**. • The Panel **recommends against** routinely continuing VTE prophylaxis for patients with COVID-19 after hospital discharge, except in a clinical trial **(AIII)**. • For patients who are at high risk for VTE and low risk for bleeding, there is insufficient evidence to recommend either for or against continuing anticoagulation after hospital discharge unless another indication for VTE prophylaxis exists. **Antithrombotic Therapy for Hospitalized, Nonpregnant Adults Without Evidence of Venous Thromboembolism** • The Panel **recommends against** using anticoagulant or antiplatelet therapy to prevent arterial thrombosis outside of the usual standard of care for patients without COVID-19 **(AIII)**. • In hospitalized patients, **low-molecular-weight heparin** (LMWH) or **unfractionated heparin** (UFH) is preferred over oral anticoagulants, because these 2 types of heparin have shorter half-lives and the effect can be reversed quickly, can be administered intravenously or subcutaneously, and have fewer drug-drug interactions **(AIII)**. • When heparin is used, LMWH is preferred over UFH. *For adults who require low-flow oxygen and do not require intensive care unit (ICU)-level care:* • The Panel recommends using a **therapeutic dose** of heparin for patients with D-dimer levels above the upper limit of normal, who require low-flow oxygen, and who do not have an increased bleeding risk **(CIIa)**.   • Contraindications for the use of therapeutic anticoagulation in patients with COVID-19 are a platelet count <50 x 109/L, hemoglobin <8 g/dL, the need for dual antiplatelet therapy, bleeding within the past 30 days that required an emergency department visit or hospitalization, history of a bleeding disorder, or an inherited or active acquired bleeding disorder. This list is based on the exclusion criteria from clinical trials; patients with these conditions have an increased risk of bleeding. • In patients without VTE who have begun a therapeutic dose of heparin, treatment should continue for 14 days or until hospital discharge, whichever comes first. • The Panel recommends using a **prophylactic dose** of heparin for patients who are not receiving a therapeutic dose of heparin, unless a contraindication exists **(AIIb)**.

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Summary Recommendations, continued
• The Panel **recommends against** the use of a **therapeutic dose** of oral anticoagulants for VTE prophylaxis or prevention of COVID-19 progression, except in a clinical trial **(AIIa)**. • There is currently insufficient evidence to recommend either for or against the use of thrombolytics for COVID-19. • The Panel **recommends against** the use of antiplatelet therapy to prevent COVID-19 progression or death in noncritically ill patients **(BIIa)**. *For adults who require ICU-level care, including those receiving high-flow oxygen:* • The Panel recommends using a **prophylactic dose** of heparin as VTE prophylaxis, unless a contraindication exists **(AI)**. • The Panel **recommends against** the use of an **intermediate dose** (e.g., **enoxaparin** 1 mg/kg once daily) or a **therapeutic dose** of anticoagulation for VTE prophylaxis, except in a clinical trial **(BI)**. • For patients who start on a therapeutic dose of heparin in a non-ICU setting due to COVID-19 and then transfer to the ICU, the Panel recommends switching from the therapeutic dose to a **prophylactic dose** of heparin, unless VTE is confirmed **(BIII)**. • There is insufficient evidence for the Panel to recommend either for or against antiplatelet therapy in critically ill patients with COVID-19. **Hospitalized Children** • For hospitalized children with COVID-19, indications for VTE prophylaxis should be the same as those for children without COVID-19 **(BIII)**. **Special Considerations During Pregnancy and Lactation** • The Panel recommends that pregnant patients who are receiving anticoagulant or antiplatelet therapies for underlying conditions continue these medications after they receive a diagnosis of COVID-19 **(AIII)**. • The Panel recommends using a **prophylactic dose** of anticoagulation for pregnant patients hospitalized for manifestations of COVID-19, unless otherwise contraindicated **(BIII)**. • Because pregnant patients have not been included in most clinical trials evaluating therapeutic anticoagulation in the setting of COVID-19, there is currently insufficient evidence to recommend either for or against therapeutic anticoagulation for pregnant patients with COVID-19 without evidence of VTE. • Like for nonpregnant patients, VTE prophylaxis after hospital discharge is not routinely recommended for pregnant patients **(BIII)**. Decisions to continue VTE prophylaxis in the pregnant or postpartum patient after discharge should be individualized, with consideration of concomitant VTE risk factors. • The use of anticoagulation therapy 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 **(AIII)**. • **UFH**, **LMWH**, 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 who require VTE prophylaxis or treatment **(AIII)**.
Rating of Recommendations: A = Strong; B = Moderate; C = Weak **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

COVID-19 has been associated with inflammation and a prothrombotic state, with increases in fibrin, fibrin degradation products, fibrinogen, and D-dimer levels.[1,2] In some studies, elevations in these markers have been associated with worse clinical outcomes.[3,4]

Studies have reported varying incidences of venous thromboembolism (VTE) in patients with COVID-19. A meta-analysis of studies of hospitalized patients with COVID-19 treated with VTE prophylaxis 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

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did not (9.5%; 95% CI, 7.5–11.7). In randomized controlled trials conducted prior to the pandemic, the incidence of VTE in hospitalized patients without COVID-19 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 patients without COVID-19 who received a prophylactic dose of 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]

Guidelines about the use of antithrombotic therapy in patients with COVID-19 have been released by multiple organizations, including the American College of Chest Physicians,[13] American Society of Hematology,[14] Anticoagulation Forum,[15] International Society on Thrombosis and Haemostasis,[16] Italian Society for Haemostasis and Thrombosis,[17] National Institute for Health and Care Excellence (NICE),[18] and Royal College of Physicians.[19]

The guidelines referenced above agree that hospitalized, nonpregnant patients with COVID-19 should receive, at a minimum, a prophylactic dose of anticoagulation to prevent VTE. The NICE guideline recommendation states, "Consider a treatment dose of a low molecular weight heparin (LMWH) for young people and adults with COVID-19 who need low-flow oxygen and who do not have an increased bleeding risk." Results from clinical trials that assess the safety and efficacy of different anticoagulant doses and strategies have provided further information on antithrombotic strategies for patients with COVID-19.

Chronic Anticoagulant or Antiplatelet Therapy

The COVID-19 Treatment Guidelines Panel (the Panel) recommends that hospitalized patients with COVID-19 who are receiving anticoagulant or antiplatelet therapy for underlying medical conditions continue this treatment unless significant bleeding develops, or other contraindications are present **(AIII)**. Outpatients with COVID-19 who are receiving warfarin and are in isolation and unable to have international normalized ratio monitoring may be candidates for switching to direct oral anticoagulant therapy, except in settings where substitution would be clinically inappropriate, such as for patients with a mechanical heart valve, a ventricular assist device, valvular atrial fibrillation, or antiphospholipid antibody syndrome or who are lactating.

Screening and Evaluation for Venous Thromboembolism

VTE guidelines for patients without COVID-19 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.[20] Although the incidence of thromboembolic events, especially pulmonary emboli, can be high among hospitalized patients with COVID-19, no published data demonstrate the clinical utility of using lower extremity ultrasound as routine surveillance for deep vein thrombosis in this population.

- In patients with COVID-19 who have no signs or symptoms of VTE, there is currently insufficient evidence to recommend either for or against routine VTE screening, regardless of the patient's coagulation markers.
- For hospitalized patients with COVID-19 who experience rapid deterioration of pulmonary, cardiac, or neurological function or sudden, localized loss of peripheral perfusion, the Panel recommends evaluating the patients for thromboembolic disease **(AIII)**.

Managing Antithrombotic Therapy in Patients With COVID-19

The Panel recommends that when diagnostic imaging is not possible, patients with COVID-19 who are highly suspected to have thromboembolic disease be managed with therapeutic anticoagulation **(AIII)**.

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The Panel recommends that patients with COVID-19 who require extracorporeal membrane oxygenation (ECMO) or continuous renal replacement therapy or who have thrombosis related to catheters or extracorporeal filters be treated with antithrombotic therapy as per the standard institutional protocols for those without COVID-19 **(AIII)**.

Selection of Anticoagulant or Antiplatelet Drugs

Whenever anticoagulant or antiplatelet therapy is used, potential drug-drug interactions with other concomitant drugs must be considered. The University of Liverpool has collated a list of drug interactions. In hospitalized, critically ill patients, **LMWH** or **unfractionated heparin (UFH)** is preferred over oral anticoagulants, because these 2 types of heparin have shorter half-lives and the effect can be reversed quickly, can be administered intravenously or subcutaneously, and have fewer drug-drug interactions **(AIII)**.

Management of Nonhospitalized Patients

The ACTIV-4b placebo-controlled, randomized trial evaluated the efficacy of aspirin versus prophylactic (2.5 mg) or therapeutic (5 mg) doses of apixaban to prevent thromboembolic events, hospitalization, and death in outpatients with COVID-19 aged >40 years. The trial was stopped in June 2021 due to a low event rate (1 patient each in the placebo, aspirin, and apixaban 2.5 mg arms and 2 patients in the apixaban 5 mg arm) after randomization of 657 symptomatic outpatients. The median time from randomization to study treatment was 3 days, and 22 participants were hospitalized for COVID-19 prior to initiation of study drug.[21] It is not known whether patients with previous VTE events or inherited thrombophilias were included in this trial. For nonhospitalized patients with COVID-19, the Panel **recommends against** the use of anticoagulants and antiplatelet therapy for the prevention of VTE or arterial thrombosis unless the patient has other indications for the therapy or is participating in a clinical trial **(AIIa)**.

Management of Hospitalized Patients

Several studies have evaluated the risks and benefits of prophylactic or therapeutic doses of anticoagulants in patients with COVID-19. Observational studies and clinical trials have examined the effects of anticoagulation on mortality, progression of COVID-19, thrombosis, and bleeding. Some of these studies are outlined below (visit ClinicalTrials.gov for a current list of trials). Observational studies are included here only when evidence from clinical trials is not available.

Prophylactic-Dose of Anticoagulation Versus No Anticoagulation—Observational Cohort

An observational study of 4,297 veterans hospitalized with COVID-19 evaluated the benefit of prophylactic anticoagulation. A prophylactic dose of anticoagulation was administered to 3,627 patients with COVID-19 within 24 hours of hospital admission. An inverse probability of treatment weighted analysis showed a cumulative 30-day mortality of 14% among veterans who received prophylactic anticoagulation and 19% among patients who were not treated with anticoagulation (HR 0.73; 95% CI, 0.66–0.81). Participants treated with the prophylactic dose did not have a significant difference in risk of bleeding that required transfusion when compared with participants who were not treated (HR 0.87; 95% CI, 0.71–1.05). Overall, the study demonstrated that patients with COVID-19 may benefit from a prophylactic dose of anticoagulation.[22]

Therapeutic Versus Prophylactic Doses of Heparin in Hospitalized Patients Who Do Not Require Intensive Care Unit-Level Care

Several randomized controlled trials have evaluated the role of therapeutic doses of heparin in reducing VTE events or mortality in patients hospitalized for COVID-19.

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Three open-label randomized controlled trials (the large ATTACC/ACTIV-4a/REMAP-CAP multiplatform trial and the smaller RAPID and HEP-COVID trials) compared therapeutic doses of heparin to prophylactic or intermediate doses of the anticoagulant in selected hospitalized patients who did not require intensive care. Clinical data for these trials are summarized in Table 5a. The inclusion and exclusion criteria for these studies varied, but most included a need for supplemental oxygen and no risk of a major bleeding event. In the larger multiplatform trial, therapeutic doses of heparin increased organ support-free days but did not significantly affect mortality or length of hospitalization when compared with prophylactic doses of heparin.[23]

The RAPID trial enrolled patients with elevated D-dimer levels and hypoxemia. The patients were randomized to receive therapeutic or prophylactic doses of heparin. There was no statistically significant difference between the arms for the primary endpoint, which was a composite of intensive care unit (ICU) admission, noninvasive or mechanical ventilation, or death by Day 28. However, the therapeutic dose of heparin reduced all-cause death, a secondary outcome.[24]

The HEP-COVID trial enrolled patients who required supplemental oxygen and had a D-dimer value >4 times the upper limit of normal (ULN) or a sepsis-induced coagulopathy score of ≥4. There were significantly fewer occurrences of the primary endpoint of VTE, arterial thromboembolism, or all-cause death within 32 days of randomization in the therapeutic LMWH arm than in the prophylactic LMWH arm, but there was no difference between arms for the outcome of death within 32 days.[25] Results from smaller randomized trials, single-center studies, and observational studies have also been published.

Given the results of the ATTACC/ACTIV-4a/REMAP-CAP, RAPID, and HEP-COVID trials conducted among hospitalized, nonpregnant adults with COVID-19 who did not require ICU-level care and without evidence of VTE:

- The Panel recommends using a **therapeutic dose** of heparin for patients with D-dimer levels above the ULN who require low-flow oxygen and who do not have an increased bleeding risk **(CIIa)**.
  - Based on clinical trial exclusion criteria, contraindications for use of therapeutic anticoagulation for patients with COVID-19 are a platelet count <50 x 109/L, hemoglobin <8 g/dL, the need for dual antiplatelet therapy, bleeding within the past 30 days that required an emergency department visit or hospitalization, history of a bleeding disorder, or an inherited or active, acquired bleeding disorder.
- LMWH is preferred over UFH because of its decreased administrative burden and because LMWH was the predominant form of heparin used in the clinical trials for COVID-19.
- In patients without VTE who have begun a therapeutic dose of heparin, treatment should continue for 14 days or until hospital discharge, whichever comes first.
- Patients with predicted hospitalizations of <72 hours were excluded from the multiplatform trial. The risk/benefit ratio of therapeutic doses of anticoagulation for short hospital stays is not known.
- The Panel recommends using a **prophylactic dose** of heparin for patients who do not meet the criteria for receiving therapeutic heparin or are not receiving a therapeutic dose of heparin for other reasons, unless a contraindication exists **(AIIb)**.
- The Panel **recommends against** the use of a **therapeutic dose** of oral anticoagulants for VTE prophylaxis or prevention of COVID-19 progression, except in a clinical trial **(AIIa)**.
- There is currently insufficient evidence to recommend either for or against the use of thrombolytics for COVID-19.

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Prophylactic Versus Intermediate or Therapeutic Doses of Heparin in Hospitalized Patients Who Require Intensive Care Unit-Level Care

Several randomized controlled trials have evaluated the role of therapeutic doses of heparin in reducing VTE events or mortality in patients in the ICU setting. Clinical data for these trials are summarized in Table 5a.

For the composite endpoint of adjudicated VTE, arterial thrombosis, ECMO, or all-cause mortality, the INSPIRATION trial found no difference between patients in the ICU treated with an intermediate dose of anticoagulation (enoxaparin 1 mg/kg daily) and those who received a prophylactic dose (45.7% vs. 44.1%; OR 1.06; 95% CI, 0.76–1.48). Major bleeding occurred in 2.5% of patients in the intermediate-dose anticoagulation arm compared with 1.4% of patients who received the prophylactic dose. Overall, there was no significant benefit of receiving an intermediate dose of anticoagulation for patients with COVID-19 in the ICU.[26]

A multiplatform randomized control trial (REMAP-CAP/ACTIV-4a/ATTACC) compared the effectiveness of a therapeutic dose of heparin or LMWH with usual care in reducing the number of organ support-free days among critically ill patients with COVID-19.[27] All 3 trials were stopped for futility. Heparin doses in the usual care arm varied. The median number of organ support-free days was 3 days (IQR -1 to 16) for patients who received a therapeutic dose of anticoagulation and 4 days (IQR -1 to 16) for patients who received usual care. The likelihood of survival to hospital discharge did not differ between arms (63% therapeutic arm vs. 65% usual care arm; aOR 0.84; 95% CrI, 0.64–1.11). Major bleeding occurred in 4% of participants receiving therapeutic anticoagulation and in 2% of participants receiving usual care. Therapeutic doses of heparin showed no significant benefit for patients with COVID-19 admitted to the ICU.

Given the results of these trials, for hospitalized, nonpregnant adults with COVID-19 who require ICU level-care and who do not have documented or suspected VTE:

- The Panel recommends using a **prophylactic dose** of heparin as VTE prophylaxis, unless a contraindication exists **(AI)**.
- For patients who start on a therapeutic dose of heparin in a non-ICU setting due to COVID-19 and then transfer to the ICU, the Panel recommends switching from the therapeutic dose to a **prophylactic dose** of heparin, unless VTE is confirmed **(BIII)**.
- The Panel **recommends against** the use of an **intermediate dose** (e.g., **enoxaparin** 1 mg/kg daily) or a **therapeutic dose** of anticoagulation for VTE prophylaxis, except in a clinical trial **(BI)**.

Rivaroxaban Versus Usual Care in Hospitalized Patients With Elevated D-Dimer Levels

The ACTION trial randomized adults hospitalized with COVID-19 and elevated D-dimer levels (defined as above the laboratory ULN) to receive rivaroxaban 20 mg daily for 30 days or usual care[28] (see Table 5a for a summary of clinical data for this trial). No statistical difference was found for the composite endpoint of time to death, hospitalization duration, and oxygen use duration (hierarchical analysis; win ratio 0.86; 95% CI, 0.59–1.22) or for the individual components. The probability of clinically relevant nonmajor bleeding was greater with rivaroxaban (5% rivaroxaban arm vs. 1% usual care arm; relative risk 5.23; 95% CI, 1.54–17.77), but for major bleeding events the difference between arms was not significant (3% rivaroxaban arm vs. 1% usual care arm; relative risk 2.45; 95% CI, 0.78–7.73).

Given the lack of benefit and the increased risk of bleeding events, the Panel **recommends against** the use of a **therapeutic dose** of oral anticoagulation for VTE prophylaxis and prevention of COVID-19 progression, except in a clinical trial **(AIIa)**.

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Antiplatelet Therapy Versus Usual Care in Hospitalized Patients

Multiple retrospective cohort studies suggested reduced in-hospital mortality in patients treated with aspirin either before or within 24 hours of admission.[29-31] Results from those studies have been summarized in meta-analysis.[32] These epidemiologic studies used propensity scoring or adjustment for confounders, but indication bias could not be fully removed. Thus, randomized controlled trials are needed to further define the role of aspirin and other antiplatelet therapy as an adjunctive treatment in the management of COVID-19.

The RECOVERY trial randomized 7,351 hospitalized adults with COVID-19 to usual care plus aspirin 150 mg per day and 7,541 patients to usual care only (see Table 5b).[33] At enrollment, 33% of the patients required noninvasive or mechanical ventilation. Mortality at 28 days was 17% in both arms (rate ratio 0.96; 95% CI, 0.89–1.04). Results were similar in all prespecified subgroups. Among participants not receiving mechanical ventilation at baseline, there was no difference in progression to mechanical ventilation or death (21% aspirin arm vs. 22% usual care arm; rate ratio 0.96; 95% CI, 0.90–1.03). Among those treated with aspirin, the incidence of thrombotic events was lower (4.6% vs. 5.3%; absolute difference 0.6%; SE 0.4%), and the incidence of major bleeding events was higher (1.6% vs. 1.0%; absolute difference 0.6%; SE 0.2%). Overall, in this large trial of hospitalized patients with COVID-19, aspirin was associated with increased bleeding events and did not reduce mortality.

The ACTIV-4a trial evaluated P2Y12 inhibitor therapy plus a therapeutic dose of heparin versus therapeutic heparin alone in hospitalized patients with COVID-19. In this study, enrollment in the noncritically ill cohort was stopped due to futility because the combination therapy did not improve the number of organ support-free days.[34] Trial limitations include an open-label design, use of different P2Y12 inhibitors, and a relatively small trial size.

Based on the findings from the ACTIV-4a and RECOVERY trials, the Panel **recommends against** the use of antiplatelet therapy to prevent COVID-19 progression or death in noncritically ill patients **(BIIa)**.

The REMAP-CAP study team conducted an open-label, adaptive randomized controlled trial of aspirin (n = 565), a P2Y12 inhibitor (n = 455), or no antiplatelet therapy (n = 529) in critically ill patients with COVID-19 (see Table 5b).[35] Treatment was continued for 14 days or until hospital discharge, whichever came first. The aspirin and P2Y12 inhibitor arms were pooled for analysis because the criteria for equivalence were met. The trial was stopped due to futility, as the median of organ support-free days did not differ between the antiplatelet and control arms (7 days [IQR 1–16 days]; 95.7% posterior probability of futility). Survival to hospital discharge was numerically, but not statistically, different between the arms (antiplatelet arm, 723 of 1,011 participants [71.5%] vs. control arm, 354 of 521 participants [67.9%]; median aOR, 1.27; 95% CrI, 0.99–1.62). A significantly larger proportion of participants in the antiplatelet arm than in the control arm had survived at 90 days (median aHR 1.22; 95% CrI, 1.06–1.40). Antiplatelet therapy was associated with increased major bleeding (2.1% in antiplatelet arm vs. 0.4% in control arm; aOR 2.97; 95% CrI, 1.23–8.28; adjusted absolute risk difference 0.8%; 95% CrI, 0.1%–2.7%).

In summary, in the RECOVERY trial, aspirin therapy was not associated with reduced mortality in the subgroups of patients requiring noninvasive or mechanical ventilation at baseline. In the REMAP-CAP trial, 90-day survival was greater among critically ill patients with COVID-19 who received antiplatelet therapy, but there was no difference between the antiplatelet and control arms in the number of organ support-free days. In both studies, antiplatelet therapy was associated with an increased risk of bleeding. Because of these results, there is insufficient evidence for the Panel to recommend either for or against antiplatelet therapy in critically ill patients with COVID-19. Participation in clinical trials is encouraged.

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Thrombolytic Therapy

Clinical trials are evaluating the use of thrombolysis on mortality and the progression of COVID-19 illness. There is currently insufficient evidence to recommend either for or against the use of thrombolytic agents for VTE prophylaxis for hospitalized patients with COVID-19 outside of a clinical trial.

Hospitalized Children

A recent meta-analysis of publications on COVID-19 in children did not discuss VTE.[36] Indications for VTE prophylaxis in hospitalized children with COVID-19 should be the same as those for hospitalized children without COVID-19 **(BIII)**.

Patients Discharged From the Hospital

For 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.[37,38] Inclusion criteria for the trials that studied post-discharge VTE prophylaxis included:

- A VTE risk score of ≥4 on the modified International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) tool,[39] *or*
- A VTE risk score ≥2 on the modified IMPROVE tool[40] and a D-dimer level >2 times ULN.[37]

The MICHELLE trial randomized 320 patients with COVID-19 who had an IMPROVE score of ≥4 or a score of 2 to 3 with a D-dimer >500 ng/mL to rivaroxaban 10 mg orally daily or no anticoagulation for 35 days.[41] The primary outcome was symptomatic VTE, fatal pulmonary embolism, symptomatic arterial thromboembolism, cardiovascular death, or asymptomatic VTE detected by screening imaging at day 35. Five patients (3%) treated with rivaroxaban and 15 patients (9%) who did not receive anticoagulation experienced a thrombotic event (relative risk 0.33; 95% CI, 0.13–0.90). One patient who received rivaroxaban and 10 patients who did not receive anticoagulation experienced symptomatic events. No major bleeding events occurred, and 2 patients had clinically relevant, nonmajor bleeding in each arm. The open-label design and the inclusion of asymptomatic events detected by screening ultrasound and computed tomography may have biased the results. In addition, two-thirds of the screened patients did not meet trial eligibility, which limits generalizability.

The Panel **recommends against** routinely continuing VTE prophylaxis for patients with COVID-19 after hospital discharge, except in a clinical trial **(AIII)**. For patients who are at high risk for VTE and low risk for bleeding, there is insufficient evidence to recommend either for or against continuing anticoagulation after hospital discharge unless another indication for VTE prophylaxis exists. The decision to prescribe post-discharge VTE prophylaxis for patients with COVID-19 should include consideration of an individual patient's risk factors for VTE, 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.[42] 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.[43-45] The American College of Obstetricians and Gynecologists (ACOG) advises that, although there are no data for or against

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thromboprophylaxis in the setting of COVID-19 in pregnancy, VTE prophylaxis can reasonably be considered for pregnant individuals hospitalized with COVID-19, particularly for those who have severe disease.[46] If there are no contraindications to use, the Society for Maternal-Fetal Medicine recommends prophylactic heparin or LMWH in critically ill or mechanically ventilated pregnant patients.[47] 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.[48,49] If delivery is imminent, or if there are other risks for bleeding, the risk of bleeding may outweigh the potential benefit of VTE prophylaxis in pregnancy.

Outside of pregnancy, D-dimer levels have been used to stratify VTE risk. However, physiologic increases in D-dimer levels may occur during pregnancy, making elevated D-dimer values an unreliable predictor that should not be used to evaluate VTE risk during pregnancy in the setting of COVID-19.[50-52]

In general, the preferred anticoagulants for use during pregnancy are heparin compounds. Because of its reliability and ease of administration, LMWH is recommended rather than UFH for the prevention and treatment of VTE in pregnancy.[49] Direct-acting anticoagulants are not routinely recommended during pregnancy because of a lack of safety data for pregnant individuals.[48] The use of warfarin to prevent or treat VTE should be avoided in pregnant individuals regardless of their COVID-19 status, especially during the first trimester due to the concern for teratogenicity.

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

- The Panel recommends that pregnant patients who are receiving anticoagulant or antiplatelet therapies for underlying conditions continue these medications after they receive a diagnosis of COVID-19 **(AIII)**.
- The Panel recommends using a **prophylactic dose** of anticoagulation for pregnant patients hospitalized for manifestations of COVID-19, unless otherwise contraindicated **(BIII)**.
- Because pregnant patients have not been included in most clinical trials evaluating therapeutic anticoagulation in the setting of COVID-19, there is currently insufficient evidence to recommend either for or against therapeutic anticoagulation for pregnant patients with COVID-19 without evidence of VTE.
- Like for nonpregnant patients, VTE prophylaxis after hospital discharge is not routinely recommended for pregnant patients **(BIII)**. Decisions to continue VTE prophylaxis in the pregnant or postpartum patient after discharge should be individualized, with consideration of concomitant VTE risk factors.
- The use of anticoagulation therapy 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 **(AIII)**.
- **UFH**, **LMWH**, 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 who require VTE prophylaxis or treatment **(AIII)**.

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Table 5a. Antithrombotic Therapy: Selected Clinical Data

Last Updated: February 24, 2022

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

Methods	Results	Limitations and Interpretation
ATTACC/ACTIV-4a/REMAP-CAP: Multiplatform, Open-Label RCT of Therapeutic Anticoagulation in Noncritically Ill, Hospitalized Patients With COVID-19 in 9 Countries[1]		

Key Inclusion Criteria:
• Hospitalized with laboratory-confirmed SARS-CoV-2 infection without need for HFNC oxygen, NIV, MV, vasopressors, or inotropes
Key Exclusion Criteria:
• Discharge expected ≤72 hours
• Requirement for therapeutic anticoagulation or dual antiplatelet therapy
• High bleeding risk
Interventions:
• Therapeutic UFH or LMWH for 14 days or until discharge, whichever comes first (n = 1,190)
• SOC (n = 1,054)
Primary Endpoint:
• Organ support-free days at Day 21, evaluated on an ordinal scale
Key Secondary Endpoints:
• Survival until hospital discharge
• Hospital LOS
• Thrombosis or major bleeding
	Participant Characteristics:
	• Median age 59 years; 59% men; median BMI 30
	• 52% with HTN; 30% with DM; 11% with CVD
	• 66% required low-flow oxygen
	• D-dimer:
	  • 48.4% <2 times ULN
	  • 28.4% ≥2 times ULN
	  • 23.1% unknown
	• 62% on corticosteroids; 36% on RDV
	Primary Outcomes:
	• Organ support-free days: therapeutic anticoagulation superior to SOC (aOR 1.27; 95% CrI, 1.03–1.58; 99% posterior probability)
	• Survival until hospital discharge without organ support: 4% absolute difference favoring therapeutic anticoagulation arm (95% CrI, 0.5–7.2)
	• Outcome consistent across D-dimer stratum
	Secondary Outcomes:
	• Survival until hospital discharge: 92% in both arms
	• Hospital LOS: no difference between arms (aOR 1.03; 95% CrI, 0.94–1.13)
	• Thrombosis: 1% in therapeutic arm vs. 2% in SOC arm
	• Major bleeding: 2% in therapeutic arm vs. 1% in SOC arm
		Key Limitations:
		• Open-label study
		• Anticoagulation dose varied in SOC arm (27% received intermediate-dose thromboprophylaxis).
		• Studies had different criteria for ICU care and expected hospital LOS.
		• Only enrolled 17% of screened patients
		Interpretation:
		• Therapeutic heparin increased organ support-free days and decreased the number of patients requiring organ support.
		• Therapeutic heparin did not significantly affect hospital LOS or the number of major thrombosis events or deaths.
		• Major bleeds occurred 1% more frequently in therapeutic arm than in SOC arm.

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Methods	Results	Limitations and Interpretation
RAPID: Open-Label RCT of Therapeutic Heparin in Moderately Ill, Hospitalized Patients With COVID-19 in 6 Countries[2]		

Key Inclusion Criteria:
• Hospitalized with COVID-19 and D-dimer ≥2 times ULN or any elevated D-dimer level and SpO_2 ≤93% on room air
• Hospitalized <5 days
Key Exclusion Criteria:
• Indication for therapeutic anticoagulation
• Dual antiplatelet therapy
• High bleeding risk
Interventions:
• Therapeutic UFH or LMWH for 28 days or until discharge or death (n = 228)
• Prophylactic UFH or LMWH for 28 days or until discharge or death (n = 237)
Primary Endpoint:
• Composite of ICU admission, NIV or MV, or death up to 28 days
Key Secondary Endpoints:
• All-cause death
• Mean organ support-free days
• VTE
• Major bleeding event
• Mean hospital-free days alive
	Participant Characteristics:
	• Median age 60 years; 57% men; mean BMI 30
	• 48% with HTN; 34% with DM; 7% with CVD
	• 91% had hypoxia; 6% received HFNC oxygen
	• D-dimer:
	  • 49% <2 times ULN
	  • 51% ≥2 times ULN
	• 69% on corticosteroids
	Primary Outcome:
	• ICU admission, NIV or MV, or death: 16% in therapeutic arm vs. 22% in prophylactic arm (OR 0.69; 95% CI, 0.43–1.10)
	Secondary Outcomes:
	• All-cause death: 2% in therapeutic arm vs. 8% in prophylactic arm (OR 0.22; 95% CI, 0.07–0.65)
	• Mean organ support-free days: 26 days in therapeutic arm vs. 24 days in prophylactic arm (OR 1.41; 95% CI, 0.9–2.21)
	• No difference between arms for VTE (1% in therapeutic arm vs. 3% in prophylactic arm) or major bleeding (1% in therapeutic arm vs. 2% in prophylactic arm)
	• Mean hospital-free days alive: 20 days in therapeutic arm vs. 18 days in prophylactic arm (OR 1.09; 95% CI, 0.79–1.50)
		Key Limitations:
		• Open-label study
		• Only enrolled 12% of screened patients
		Interpretation:
		• Compared to prophylactic heparin, therapeutic heparin reduced mortality (a secondary endpoint) but had no effects on the composite primary endpoint of ICU admissions or the need for NIV or MV, or death up to 28 days.
		• Major bleeding and VTE events were not different in the therapeutic and prophylactic arms.

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Methods	Results	Limitations and Interpretation
HEP-COVID: Open-Label RCT of Therapeutic Heparin in High-Risk, Hospitalized Patients With COVID-19 in the United States[3]		

Key Inclusion Criteria:
• Hospitalized with supplemental oxygen
• D-dimer >4 times ULN or sepsis-induced coagulopathy score of ≥4
• Hospitalized <72 hours
Key Exclusion Criteria:
• Indication for therapeutic anticoagulation
• Dual antiplatelet therapy
• High bleeding risk
• CrCl <15 mL/min
Interventions:
• Therapeutic LMWH until hospital discharge or primary endpoint met (n = 129)
• Usual care of prophylactic or intermediate-dose LMWH until hospital discharge or primary endpoint met (n = 124)
Primary Endpoint:
• Composite of VTE, ATE, or death of any cause within 32 days of randomization
Key Safety Endpoint:
• Major bleeding
	Participant Characteristics:
	• Median age 67 years; 54% men; mean BMI 30
	• 60% with HTN; 37% with DM; 7% with CVD
	• 64% received oxygen via nasal cannula; 15% received high-flow oxygen or NIV; 5% received MV
	• 80% on corticosteroids
	Primary Outcomes:
	• Composite of VTE, ATE, and death within 32 days: 29% in therapeutic arm vs. 42% in usual care arm (relative risk 0.68; 95% CI, 0.49–0.96)
	  • Death: 19% in therapeutic arm vs. 25% in usual care arm (relative risk 0.78; 95% CI, 0.49–1.23)
	  • Thrombotic events: 11% in therapeutic arm vs. 29% in usual care arm (relative risk 0.37; 95% CI, 0.21–0.66
	• Non-ICU stratum composite of VTE, ATE, or death within 32 days: 17% in therapeutic arm vs. 36% in usual care arm (relative risk 0.46; 95% CI, 0.27–0.81)
	Safety Outcomes:
	• Major bleeding: 5% in therapeutic arm vs. 2% in usual care arm (relative risk 2.88, 95% CI, 0.59–14.02)
	• Non-ICU stratum major bleeding: 2% in both arms
		Key Limitations:
		• Open-label study
		• Only enrolled 2% of screened patients
		Interpretation:
		• Compared to usual care, therapeutic LMWH reduced the incidence of VTE, ATE, and death.
		• For patients not in the ICU, therapeutic LMWH significantly reduced thrombotic events and did not increase major bleeding.

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Methods	Results	Limitations and Interpretation
ACTION: Open-Label RCT of Therapeutic Oral Anticoagulation (Rivaroxaban) in Hospitalized Patients With COVID-19 in Brazil[4]		

Key Inclusion Criteria:
• Hospitalized for COVID-19 with elevated D-dimer level
• Symptoms for ≤14 days
Key Exclusion Criteria:
• Indication for therapeutic anticoagulation
• CrCl <30 mL/min
• P2Y12 inhibitor therapy or aspirin >100 mg
• High bleeding risk
Interventions:
• Therapeutic anticoagulation for 30 days: rivaroxaban 15 mg or 20 mg daily; if clinically unstable, enoxaparin 1 mg/kg twice daily or UFH (n = 311)
• Usual care prophylactic anticoagulation with enoxaparin or UFH during hospitalization (n = 304)
Primary Endpoint:
• Hierarchical composite of time to death, hospital duration, and oxygen use duration through Day 30
Key Secondary Endpoints:
• Thrombosis, with and without all-cause death
• Mortality
• Bleeding events
	Participant Characteristics:
	• Median age 57 years; 60% men; mean BMI 30
	• 49% with HTN; 24% with DM; 5% with coronary disease
	• Critically ill: 7% in therapeutic arm; 5% in usual care arm
	• 75% required oxygen: 60% low-flow oxygen; 8% HFNC oxygen; 1% NIV; 6% MV
	• 83% on corticosteroids
	Primary Outcomes:
	• Composite of time to death, hospital duration, and oxygen use duration: no difference between arms (win ratio 0.86; 95% CI, 0.59–1.22)
	Secondary Outcomes:
	• No difference between therapeutic and prophylactic arms:
	  • Mortality: 11% vs. 8%
	  • Thrombosis: 7% vs. 10%
	• Any bleeding: 12% in therapeutic arm vs. 3% in usual care arm
	• Major bleeding: 3% in therapeutic arm vs. 1% in usual care arm
	• Clinically relevant, nonmajor bleeding: 5% in therapeutic arm vs. 1% in usual care arm
		Key Limitations:
		• Open-label study
		• Only enrolled 18% of screened patients
		• Longer duration of anticoagulation in the rivaroxaban arm (30 days) than the prophylactic anticoagulation arm (mean duration = 8 days)
		Interpretation:
		• When compared with usual care, therapeutic rivaroxaban did not reduce mortality, hospital duration, oxygen use duration, or thrombosis.
		• Patients who received therapeutic rivaroxaban had more clinically relevant nonmajor bleeding than those who received usual care.
		• The longer duration of therapy in the rivaroxaban arm may have influenced the difference in bleeding events.

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Methods	Results	Limitations and Interpretation
REMAP-CAP/ACTIV-4a/ATTACC: Multiplatform, Open-Label RCT of Therapeutic Anticoagulation in Critically Ill, Hospitalized Patients With COVID-19 in 20 Countries[5]		

Key Inclusion Criteria:
• Hospitalized with severe COVID-19 and receiving HFNC oxygen, NIV, MV, ECMO, vasopressors, or inotropes
• Hospitalized <72 hours (ACTIV-4a, ATTACC) or <14 days (REMAP-CAP)
Key Exclusion Criteria:
• Discharge expected within 72 hours
• Requirement for therapeutic anticoagulation or dual antiplatelet therapy
• High bleeding risk
Interventions:
• Therapeutic UFH or LMWH for 14 days or until discharge, whichever comes first (n = 534)
• Usual care (n = 564)
Primary Endpoint:
• Organ support-free days at Day 21
Key Secondary Endpoints:
• Survival to hospital discharge
• Any thrombosis
• Composite of major thrombotic events or death
• Bleeding events
	Participant Characteristics:
	• Median age 60 years; 70% men; median BMI 30
	• 24% with chronic respiratory disease; 33% with DM; 10% with chronic kidney disease; 8% with severe CVD
	• 32% required HFNC oxygen; 38% required NIV; 29% required MV
	• 18% on vasopressors; 82% on corticosteroids; 32% on RDV
	Primary Outcome:
	• Median organ support-free days at Day 21: 4 days therapeutic arm vs. 5 days usual care arm (aOR 0.83; 95% CrI, 0.67–1.03; 99.9% posterior probability of futility; OR < 1.2)
	Secondary Outcomes:
	• No difference between therapeutic and usual care arms:
	  • Survival to hospital discharge: 63% vs. 65% (aOR 0.84; 95% CrI, 0.64–1.11)
	  • Thrombosis: 6% vs. 10%
	  • Major thrombotic events or death: 41% both arms
	  • Major bleeding events: 4% vs. 2% (aOR 1.48; 95% CrI, 0.75–3.04)
		Key Limitations:
		• Open-label study
		• Anticoagulation dose varied in usual care arm (i.e., 51% intermediate, 2% subtherapeutic, 5% therapeutic).
		• Inclusion criteria for hospital LOS and ICU-level care differed across trials.
		• Trial stopped for futility.
		Interpretation:
		• In patients requiring ICU care, therapeutic heparin did not reduce the duration of organ support or mortality.
		• Although the differences were nonsignificant, patients who received therapeutic anticoagulation had more bleeding events and fewer thrombotic events than patients who received usual care.

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Methods	Results	Limitations and Interpretation
INSPIRATION: Open-Label RCT of Intermediate-Dose Versus Prophylactic-Dose Anticoagulant in Patients in Intensive Care With COVID-19 in Iran[6]		

Key Inclusion Criteria:
• Admitted to ICU
• Hospitalized <7 days
Key Exclusion Criteria:
• Life expectancy <24 hours
• Indication for therapeutic anticoagulation
• Overt bleeding
Interventions:
• Intermediate-dose anticoagulation: enoxaparin 1 mg/kg daily (n = 276)
• Prophylactic-dose anticoagulation (n = 286)
Primary Endpoint:
• Composite of adjudicated acute VTE, ATE, ECMO, or all-cause mortality within 30 days
Key Secondary Endpoints:
• All-cause mortality
• VTE
• Bleeding event
	Participant Characteristics:
	• Median age 62 years; 58% men; median BMI 27
	• 44% with HTN; 28% with DM; 14% with coronary artery disease
	• 32% required NIV; 20% required MV
	• 23% on vasopressors; 93% on corticosteroids; 60% on RDV
	Primary Outcome:
	• Composite adjudicated acute VTE, ATE, ECMO, or all-cause mortality: 46% in therapeutic arm vs. 44% in prophylactic arm (OR 1.06; 95% CI, 0.76–1.48)
	Secondary Outcomes:
	• No difference between therapeutic and prophylactic arms:
	  • All-cause mortality: 43% vs. 41%
	  • VTE: 3% both arms
	  • Major bleeding and clinically relevant nonmajor bleeding: 6.3% vs. 3.1% (OR 2.02; 95% CI, 0.89–4.61)
		Key Limitations:
		• Open-label study
		• Not all patients received ICU-level care.
		Interpretation:
		• Intermediate-dose anticoagulation did not significantly reduce VTE and ATE, the need for ECMO, or mortality.
		• Although the difference was nonsignificant, patients who received intermediate-dose anticoagulation had more bleeding events than patients who received usual care.

Key: ATE = arterial thromboembolism; BMI = body mass index; CrCl = creatinine clearance; CVD = cardiovascular disease; DM = diabetes mellitus; ECMO = extracorporeal membrane oxygenation; HFNC = high-flow nasal cannula; HTN = hypertension; ICU = intensive care unit; LMWH = low-molecular-weight heparin; LOS = length of stay; MV = mechanical ventilation; NIV = noninvasive ventilation; the Panel = the COVID-19 Treatment Guidelines Panel; RCT = randomized controlled trial; RDV = remdesivir; SOC = standard of care; SpO_2 = oxygen saturation; UFH = unfractionated heparin; ULN = upper limit of normal; VTE = venous thromboembolism

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Table 5b. Antiplatelet Therapy: Selected Clinical Data

Last Updated: May 31, 2022

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

Methods	Results	Limitations and Interpretation
ACTIV-4a: Open-Label, Adaptive RCT of Adding a P2Y12 Inhibitor to Anticoagulant Therapy in Noncritically Ill Hospitalized Patients With COVID-19 in Brazil, Italy, Spain, and the United States[1]		

Key Inclusion Criteria:
• Laboratory-confirmed SARS-CoV-2 infection
• Any 1 of the following:
  • D-dimer level ≥2 times ULN
  • Aged 60–84 years
  • Aged <60 years with oxygen requirement >2 L/min, HTN, DM, eGFR <60 mL/min, CVD, or BMI ≥35
Key Exclusion Criteria:
• Required HFNC oxygen ≥20 L/min, NIV, MV, ECMO, vasopressors, or inotropes
• >72 hours since hospital admission
Interventions:
• Therapeutic dose of heparin plus P2Y12 inhibitor for 14 days or until discharge (n = 293)
• Therapeutic dose of heparin (usual care arm) (n = 269)
Primary Endpoints:
• Number of organ support-free days by Day 21
• Major bleeding event by Day 28
Key Secondary Endpoint:
• Major thrombotic event or death by Day 28
	Participant Characteristics:
	• Mean age 53 years; 42% women; 62% White
	• HTN: 43% in P2Y12 inhibitor arm vs. 55% in usual care arm
	• 65% on glucocorticoids; 52% on RDV; 3% on IL-6 inhibitors; 14% on aspirin
	• Median duration of P2Y12 inhibitor treatment: 6 days
	  • 63% received ticagrelor; 37% received clopidogrel
	Primary Outcomes:
	• Median number of organ support-free days: 21 in both arms (aOR 0.83; 95% CrI, 0.55–1.25; posterior probability of futility 96%)
	• Major bleeding events: 6 patients (2.0%) in P2Y12 inhibitor arm vs. 2 (0.7%) in usual care arm (aOR 3.31; 95% CI, 0.64–17.2; $P = 0.15$)
	Secondary Outcome:
	• Major thrombotic event or death by Day 28: 6.1% in P2Y12 inhibitor arm vs. 4.5% in usual care arm (aOR 1.42; 95% CI, 0.64–3.13)
		Key Limitations:
		• Open-label study
		• Study stopped early for futility
		• Different P2Y12 inhibitors used
		• Median duration of P2Y12 inhibitor use was 6 days, which may not be sufficient to observe effects.
		Interpretation:
		• Among hospitalized patients with COVID-19 who were not critically ill, adding a P2Y12 inhibitor to a therapeutic dose of heparin did not increase the number of organ support-free days.
		• Major bleeding events occurred infrequently during the study. The number of patients who experienced a major bleeding event was not significantly different between the arms.

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Methods	Results	Limitations and Interpretation
RECOVERY: Open-Label RCT of Aspirin in Hospitalized Patients With COVID-19 in Indonesia, Nepal, and the United Kingdom[2]		

Key Inclusion Criterion:
• Clinically suspected or laboratory-confirmed SARS-CoV-2 infection
Key Exclusion Criteria:
• Hypersensitivity to aspirin
• Recent history of major bleeding events
• Currently receiving aspirin or another antiplatelet treatment
Interventions:
• Aspirin 150 mg once daily until discharge (n = 7,351)
• SOC alone (n = 7,541)
Primary Endpoint:
• All-cause mortality at 28 days
Key Secondary Endpoints:
• Progression to MV or death at 28 days
• Major bleeding or thrombotic events at 28 days
	Participant Characteristics:
	• Mean age 59 years; 62% men; 75% White
	• 97% had laboratory-confirmed SARS-CoV-2 infection
	• At baseline:
	  • 33% on NIV or MV
	  • 34% on intermediate- or therapeutic-dose LMWH
	  • 60% on standard-dose LMWH
	  • 7% received no thromboprophylaxis
	  • 94% on corticosteroids; 26% on RDV; 13% on tocilizumab; 6% on baricitinib
	Primary Outcome:
	• All-cause mortality at 28 days: 17% in both arms (rate ratio 0.96; 95% CI, 0.89–1.04; $P = 0.35$)
	Secondary Outcomes:
	• Progression to MV or death at 28 days: 21% in aspirin arm vs. 22% in SOC arm (risk ratio 0.96; 95% CI, 0.90–1.03)
	• Major bleeding events at 28 days: 1.6% in aspirin arm vs. 1.0% in SOC arm ($P = 0.0028$)
	• Thrombotic events: 4.6% in aspirin arm vs. 5.3% in SOC arm ($P = 0.07$)
		Key Limitation:
		• Because of open-label design, reporting of thrombotic and major bleeding events may have influenced treatment allocation.
		Interpretation:
		• In hospitalized patients with COVID-19, the use of aspirin was not associated with reductions in 28-day mortality or the risk of progressing to MV or death.

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Methods	Results	Limitations and Interpretation
REMAP-CAP: Open-Label, Adaptive RCT of Antiplatelet Therapy in Critically Ill Patients With COVID-19 in 8 Countries in Europe and Asia[3]		

Key Inclusion Criteria:
• Clinically suspected or laboratory-confirmed SARS-CoV-2 infection
• Within 48 hours of ICU admission
Key Exclusion Criteria:
• Bleeding risk sufficient to contraindicate antiplatelet therapy
• CrCl <30 mL/min
• Receiving antiplatelet therapy or NSAID
Interventions:
• 1 of the following plus anticoagulation for 14 days or until hospital discharge, whichever came first:
  • Aspirin 75–100 mg once daily (n = 565)
  • P2Y12 inhibitor (n = 455)
  • No antiplatelet therapy (control arm) (n = 529)
Primary Endpoint:
• Number of organ support-free days by Day 21
Key Secondary Endpoints:
• Survival to hospital discharge
• Survival to Day 90
• Major bleeding event by Day 14
	Participant Characteristics:
	• Mean age 57 years; 34% women; 77% White
	• At baseline, 98% on LMWH:
	  • 19% on low-dose LMWH
	  • 59% on intermediate-dose LMWH
	  • 12% therapeutic-dose LMWH
	• 98% on steroids; 21% on RDV; 44% on tocilizumab; 11% on sarilumab
	• In P2Y12 inhibitor arm, 88.5% received clopidogrel, 1.3% received ticagrelor, 1.3% received prasugrel, and 8.8% received an unknown P2Y12 inhibitor
	Primary Outcome:
	• Data from aspirin and P2Y12 inhibitor arms were pooled and reported as "pooled antiplatelet arm" in final analysis:
	  • Median number of organ support-free days: 7 in pooled antiplatelet arm and control arm (aOR 1.02; 95% CrI, 0.86–1.23; posterior probability of futility 96%)
	Secondary Outcomes:
	• Survival to hospital discharge: 71.5% in pooled antiplatelet arm vs. 67.9% in control arm (median-adjusted OR 1.27; 95% CrI, 0.99–1.62; adjusted absolute difference 5%; 95% CrI, -0.2% to 9.5%; 97% posterior probability of efficacy)
	• Survival to Day 90: 72% in pooled antiplatelet arm vs. 68% in control arm (HR with pooled antiplatelets 1.22; 95% CrI, 1.06–1.40; 99.7% posterior probability of efficacy)
	• Major bleeding event by Day 14: 21 (2.1%) in pooled antiplatelet arm vs. 2 (0.4%) in control arm (aOR 2.97; 95% CrI, 1.23–8.28; posterior probability of harm 99.4%)
		Key Limitations:
		• Open-label study
		• Different P2Y12 inhibitors used
		• Trial stopped for futility. Because equivalence for aspirin and P2Y12 inhibitor arms was reached, these arms were pooled for analyses.
		Interpretation:
		• In critically ill patients with COVID-19, the use of aspirin or a P2Y12 inhibitor did not reduce the number of organ support-free days or in-hospital mortality.
		• Patients in pooled antiplatelet arm had more major bleeding events than those in the control arm, but they had improved survival over 90 days.

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Key: BMI = body mass index; CrCl = creatinine clearance; CVD = cardiovascular disease; DM = diabetes mellitus; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; HFNC = high-flow nasal cannula; HTN = hypertension; ICU = intensive care unit; IL = interleukin; LMWH = low-molecular-weight heparin; MV = mechanical ventilation; NIV = noninvasive ventilation; NSAID = nonsteroidal anti-inflammatory drug; the Panel = the COVID-19 Treatment Guidelines Panel; RCT = randomized controlled trial; RDV = remdesivir; SOC = standard of care; ULN = upper limit of normal

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Supplements

Last Updated: February 11, 2021

Summary Recommendations
Vitamin C • There is insufficient evidence 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 is insufficient evidence for the Panel to recommend either for or against the use of vitamin D for the treatment of COVID-19. **Zinc** • There is insufficient evidence 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 = Weak **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

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 SARS-CoV-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.

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Vitamin C

Last Updated: April 21, 2021

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 SARS-CoV-2 infection 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 is insufficient evidence 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.

Clinical Data on Vitamin C in Outpatients With COVID-19

Oral Ascorbic Acid Versus Zinc Gluconate Versus Both Agents Versus Standard of Care

In an open-label clinical trial that was conducted at two sites in the United States, outpatients with laboratory-confirmed SARS-CoV-2 infection were randomized to receive either 10 days of oral ascorbic acid 8,000 mg, zinc gluconate 50 mg, both agents, or standard of care.[3] The primary end point was the number of days required to reach a 50% reduction in the patient's symptom severity score. The study was stopped early by an operational and safety monitoring board due to futility after 40% of the planned 520 participants were enrolled (n = 214).

Patients who received standard of care achieved a 50% reduction in their symptom severity scores at a mean of 6.7 days (SD 4.4 days) compared with 5.5 days (SD 3.7 days) for the ascorbic acid arm, 5.9 days (SD 4.9 days) for the zinc gluconate arm, and 5.5 days (SD 3.4 days) for the arm that received both agents (overall $P = 0.45$). Nonserious adverse effects occurred more frequently in patients who received supplements than in those who did not; 39.5% of patients in the ascorbic acid arm, 18.5% in the zinc gluconate arm, and 32.1% in the arm that received both agents experienced nonserious adverse effects compared with 0% of patients in the standard of care arm (overall $P < 0.001$). The most common nonserious adverse effects in this study were gastrointestinal events.

The limitations of this study include the small sample size and the lack of a placebo control. In outpatients with COVID-19, treatment with high-dose zinc gluconate, ascorbic acid, or a combination of the two supplements did not significantly decrease the number of days required to reach a 50% reduction in a symptom severity score compared with standard of care.

Recommendation for Critically Ill Patients With COVID-19

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

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Rationale

There are no controlled trials that have definitively demonstrated a clinical benefit for vitamin C in critically ill patients with COVID-19, and the available observational data are inconclusive. Studies of vitamin C regimens in sepsis patients and ARDS patients have reported variable efficacy and few safety concerns.

Clinical Data on Vitamin C in Critically Ill Patients

Intravenous Vitamin C Alone in Patients With COVID-19

A pilot clinical trial in China randomized 56 adults with COVID-19 in the intensive care unit to receive intravenous (IV) vitamin C 24 g per day or placebo for 7 days. The study was terminated early due to a reduction in the number of cases of COVID-19 in China. Overall, the study found no differences between the arms in mortality, the duration of mechanical ventilation, or the change in median sequential organ failure assessment (SOFA) scores. The study reported improvements in oxygenation (as measured by the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen [PaO_2/FiO_2]) from baseline to Day 7 in the treatment arm that were statistically greater than those observed in the placebo arm (+20.0 vs. -51.9; $P = 0.04$).[4]

Intravenous Vitamin C Alone in Patients Without COVID-19

A small, three-arm pilot study compared two regimens of 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 SOFA scores and lower levels of proinflammatory markers than patients who received placebo.[5]

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.[6] 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.[7]

Intravenous Vitamin C Plus Thiamine With or Without Hydrocortisone in Critically Ill Patients Without COVID-19

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.[8,9] Subsequently, several 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 change in SOFA score on Day 3)[10,11] or the duration of shock[12] without an effect on clinical outcomes. Three other trials, including a large trial of 501 sepsis patients, found no differences in any physiologic or outcome measures between the treatment and placebo groups.[13-15]

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.[16,17]

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Vitamin D

Last Updated: April 21, 2021

Recommendation

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

Rationale

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 also overrepresented among cases of COVID-19 in the United States.[2] Vitamin D deficiency is also more common in older patients and patients with obesity and hypertension; these factors have been associated with worse outcomes in patients with COVID-19. In observational studies, low vitamin D levels have been associated with an increased risk of community-acquired pneumonia in older 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 double-blind, placebo-controlled, randomized 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]

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.

Clinical Data

Randomized Clinical Trial of Vitamin D Versus Placebo in Patients With Moderate to Severe COVID-19

In a double-blind, placebo-controlled randomized trial that was conducted at two sites in Brazil, 240 hospitalized patients with moderate to severe COVID-19 received either a single dose of 200,000 international units of vitamin D_3 or placebo.[10] Moderate to severe COVID-19 was defined as patients with a positive result on a SARS-CoV-2 polymerase chain reaction test (or compatible computed tomography scan findings) and a respiratory rate >24 breaths/min, oxygen saturation <93% on room air, or risk factors for complications. The primary outcome in this study was the length of the hospital stay.

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The median length of stay was not significantly different between the vitamin D_3 arm (7.0 days [IQR 4.0–10.0 days]) and the placebo arm (7.0 days [IQR 5.0–13.0 days]; $P = 0.59$, log-rank test). No significant differences were observed between the arms in the percentages of patients who were admitted to the intensive care unit, who required mechanical ventilation, or who died during hospitalization.

It should be noted that this study had a small sample size and enrolled participants with a variety of comorbidities and concomitant medications. The time between symptom onset and randomization was relatively long, with patients randomized at a mean of 10.3 days after symptom onset. In this study, a single, high dose of vitamin D_3 did not significantly reduce the length of stay for hospitalized patients with COVID-19.

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Zinc

Last Updated: April 21, 2021

Recommendations

- There is insufficient evidence for the COVID-19 Treatment Guidelines Panel (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)**.

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 is currently insufficient evidence 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 that was conducted at three academic medical centers in Egypt, 191 patients with laboratory-confirmed 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 arms 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

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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.

Open-Label, Randomized Trial of Zinc Versus Ascorbic Acid Versus Zinc Plus Ascorbic Acid Versus Standard of Care in Outpatients With COVID-19

In an open-label clinical trial that was conducted at two sites in the United States, outpatients with laboratory-confirmed SARS-CoV-2 infection were randomized to receive either 10 days of zinc gluconate 50 mg, ascorbic acid 8,000 mg, both agents, or standard of care. The primary end point was the number of days required to reach a 50% reduction in the patient's symptom severity score. The study was stopped early by an operational and safety monitoring board due to futility after 40% of the planned 520 participants were enrolled (n = 214).[9]

Results

- Participants who received standard of care achieved a 50% reduction in their symptom severity scores at a mean of 6.7 days (SD 4.4 days) compared with 5.5 days (SD 3.7 days) for the ascorbic acid arm, 5.9 days (SD 4.9 days) for the zinc gluconate arm, and 5.5 days (SD 3.4 days) for the arm that received both agents (overall $P = 0.45$).
- Nonserious adverse effects occurred more frequently in patients who received supplements than in those who did not; 39.5% of patients in the ascorbic acid arm, 18.5% in the zinc gluconate arm, and 32.1% in the arm that received both agents experienced nonserious adverse effects compared with 0% of patients in the standard of care arm (overall $P < 0.001$). The most common nonserious adverse effects in this study were gastrointestinal events.

Limitations

- The study had a small sample size.
- There was no placebo control.

Interpretation

In outpatients with COVID-19, treatment with high-dose zinc gluconate, ascorbic acid, or a combination of the two supplements did not significantly decrease the number of days required to reach a 50% reduction in a symptom severity score compared with standard of care.

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.[10]

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Results

- There were no significant differences in baseline characteristics between the arms. In the zinc arm, 73 patients (37.2%) died compared with 21 patients (45.7%) in the control arm. 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.[11]

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.

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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 arms 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 more often with corticosteroids and azithromycin and less often with lopinavir/ritonavir 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 Using Concomitant Medications in Patients With COVID-19

Last Updated: December 16, 2021

Summary Recommendations
• Patients with COVID-19 who are receiving concomitant medications (e.g., angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], HMG-CoA reductase inhibitors [statins], systemic or inhaled corticosteroids, nonsteroidal anti-inflammatory drugs, acid-suppressive therapy) for underlying medical conditions **should not discontinue** these medications during acute management of COVID-19 unless discontinuation is otherwise warranted by their clinical condition (**AIIa** for **ACE inhibitors and ARBs**; **AIII** for **other medications**). • The COVID-19 Treatment Guidelines Panel **recommends against** using medications off-label to treat COVID-19 if they have not been shown to be safe and effective for this indication in a clinical trial **(AIII)**.
Rating of Recommendations: A = Strong; B = Moderate; C = Weak **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

Individuals with underlying medical conditions, such as cardiovascular disease, pulmonary disease, diabetes, and malignancy, and those who receive chronic immunosuppressive therapy are at higher risk of severe illness with COVID-19. These patients are often prescribed medications to treat their underlying medical conditions.

Early in the pandemic, some of these medications, such as angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs),[1] HMG-CoA reductase inhibitors (statins),[2,3] and H-2 receptor antagonists,[4] were hypothesized to offer potential as COVID-19 therapeutic agents. Others, such as nonsteroidal anti-inflammatory agents (NSAIDs), were postulated to have negative impacts.[5] Currently, there is no evidence that discontinuing medication for underlying medical conditions offers a clinical benefit for patients with COVID-19.[6-8] For example, 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 them as directed.[9] Additionally, the American Heart Association, the Heart Failure Society of America, and the American College of Cardiology issued a joint statement that renin-angiotensin-aldosterone system antagonists, such as ACE inhibitors and ARBs, should be continued as prescribed in those with COVID-19.[10]

Therefore, patients with COVID-19 who are treated with concomitant medications for an underlying medical condition **should not discontinue** these medications during acute management of COVID-19 unless discontinuation is otherwise warranted by their clinical condition **(AIII)**. For patients with COVID-19 who require nebulized medications, precautions should be taken to minimize the potential for transmission of SARS-CoV-2 in the home and in health care settings.[11,12]

The COVID-19 Treatment Guidelines Panel **recommends against** using medications off-label to treat COVID-19 if they have not been shown to be safe and effective for this indication in a clinical trial **(AIII)**. Clinicians should refer to the Therapies section of the Guidelines for information on the medications that have been studied as potential therapeutic options for patients with COVID-19.

When prescribing medications to treat COVID-19, clinicians should always assess the patient's current medications for potential drug-drug interactions and/or additive adverse effects.[13] The decision to continue or change a patient's medications should be individualized based on their specific clinical condition.

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Special Considerations in Pregnancy

Last Updated: July 8, 2021

Key Considerations

There is current guidance from the Centers for Disease Control and Prevention, the American College of Obstetricians and Gynecologists, and the Society for Maternal-Fetal Medicine on the management of pregnant patients with COVID-19. This section of the COVID-19 Treatment Guidelines complements that guidance. The following are key considerations regarding the management of COVID-19 in pregnancy:
• Pregnant people should be counseled about the increased risk for severe disease from SARS-CoV-2 infection and receive recommendations on ways to protect themselves and their families from infection.
• If hospitalization for COVID-19 is indicated for a pregnant patient, care should be provided in a facility that can conduct maternal and fetal monitoring, when appropriate.
• Management of COVID-19 in pregnant patients should include:
  • Fetal and uterine contraction monitoring based on gestational age, when appropriate
  • Individualized delivery planning
  • A multispecialty, team-based approach that may include consultation with obstetric, maternal-fetal medicine, infectious disease, pulmonary-critical care, and pediatric specialists, as appropriate
  • In general, the therapeutic management of pregnant patients with COVID-19 should be the same as for nonpregnant patients. The COVID-19 Treatment Guidelines Panel **recommends against** withholding treatment for COVID-19 and SARS-CoV-2 vaccination from pregnant or lactating individuals because of theoretical safety concerns **(AIII)**. For details regarding therapeutic recommendations and pregnancy considerations, see General Management of Nonhospitalized Patients With Acute COVID-19 and the individual drug sections.
• Pregnant or lactating patients with COVID-19 and their clinical teams should discuss the use of investigational drugs or drugs that are approved for other indications as treatments for COVID-19. During this shared decision-making process, the patient and the clinical team should consider the safety of the medication for the pregnant or lactating individual and the fetus and the severity of maternal disease. For detailed guidance on using COVID-19 therapeutic agents during pregnancy, please refer to the pregnancy considerations subsections found in the Antiviral Therapy and Immunomodulators sections of these Guidelines.
• The decision to feed the infant breast milk while the patient is receiving therapeutic agents for COVID-19 should be a collaborative effort between the patient and the clinical team, including infant care providers. The patient and the clinical team should discuss the potential benefits of the therapeutic agent and evaluate the potential impact of pausing lactation on the future of breast milk delivery to the infant.

Rating of Recommendations: A = Strong; B = Moderate; C = Weak **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

Early in the pandemic, reports of COVID-19 disease acquired during pregnancy were limited to case series or studies that did not compare pregnant patients to age-matched, nonpregnant controls, and these reports were largely reassuring. Subsequent data have indicated that while the overall risk of severe illness is low, COVID-19 is associated with more severe disease in pregnant people than in nonpregnant people.[1] There is also an increased risk of poor obstetric outcomes among pregnant people with COVID-19, such as preterm birth.[2,3]

In November 2020, the Centers for Disease Control and Prevention (CDC) released surveillance data on outcomes in approximately 400,000 reproductive-aged women with symptomatic, laboratory-confirmed COVID-19.[1] After adjusting for age, race/ethnicity, and underlying medical conditions, pregnant women

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had significantly higher rates of intensive care unit (ICU) admission (10.5 vs. 3.9 cases per 1,000 cases; adjusted risk ratio [aRR] 3.0; 95% CI, 2.6–3.4), mechanical ventilation (2.9 vs. 1.1 cases per 1,000 cases; aRR 2.9; 95% CI, 2.2–3.8), extracorporeal membrane oxygenation (0.7 vs. 0.3 cases per 1,000 cases; aRR 2.4; 95% CI, 1.5–4.0), and death (1.5 vs. 1.2 cases per 1,000 cases; aRR 1.7; 95% CI, 1.2–2.4). The increased risk for severe disease was most significant in women aged 35 to 44 years, who were almost four times as likely to be mechanically ventilated and twice as likely to die as nonpregnant women of the same age.

Notably, among Hispanic women, pregnancy was associated with a risk of death that was 2.4 times higher (95% CI, 1.3–4.3) than the risk observed in nonpregnant Hispanic women. Racial and ethnic disparities were also seen in other reports. Among 8,207 pregnant women with COVID-19 who were reported to CDC, the proportion of those who were reported to be Hispanic (46%) and Black (22%) was higher than the proportion of Hispanic and Black women who gave birth in 2019 (24% and 15%, respectively), suggesting that pregnant people who are Hispanic or Black may be disproportionately affected by SARS-CoV-2 infection.[4]

In an ongoing systematic review that includes 192 studies to date, maternal factors that were associated with severe disease included increased maternal age (OR 1.83; 95% CI, 1.27–2.63; 3,561 women from 7 studies); a high body mass index (OR 2.37; 95% CI, 1.83–3.07; 3,367 women from 5 studies); any pre-existing maternal comorbidity, including chronic hypertension and diabetes (OR 1.81; 95% CI, 1.49–2.20; 2,634 women from 3 studies); pre-eclampsia (OR 4.21; 95% CI, 1.27–14.0; 274 women from 4 studies); and pre-existing diabetes (OR 2.12; 95% CI, 1.62–2.78; 3,333 women from 3 studies).[5] Compared with pregnant women and recently pregnant women without COVID-19, pregnant women with COVID-19 were at a higher risk of any instance of preterm birth (OR 1.47; 95% CI, 1.14–1.91; 8,549 women from 18 studies) and stillbirth (OR 2.84; 95% CI, 1.25–6.45; 5,794 women from 9 studies).

An observational cohort study of all pregnant patients at 33 U.S. hospitals with a singleton gestation and a positive result on a SARS-CoV-2 virologic test evaluated maternal characteristics and outcomes across disease severity.[6] The data suggested that adverse perinatal outcomes were more common in patients with severe or critical disease than in asymptomatic patients with SARS-CoV-2 infection, including an increased incidence of cesarean delivery (59.6% vs. 34.0% of patients; aRR 1.57; 95% CI, 1.30–1.90), hypertensive disorders of pregnancy (40.4% vs. 18.8%; aRR 1.61; 95% CI, 1.18–2.20), and preterm birth (41.8% vs. 11.9%; aRR 3.53; 95% CI, 2.42–5.14). The perinatal outcomes for those with mild to moderate illness were similar to those observed among asymptomatic patients with SARS-CoV-2 infection.

Although vertical transmission of SARS-CoV-2 is possible, current data suggest that it is rare.[7] A review of 101 infants born to 100 women with SARS-CoV-2 infection at a single U.S. academic medical center found that 2 infants (2%) had indeterminate SARS-CoV-2 polymerase chain reaction (PCR) results, which were presumed to be positive; however, the infants exhibited no evidence of clinical disease. It is reassuring that the majority of the infants received negative PCR results after rooming with their mothers and breastfeeding directly (the mothers in this study practiced appropriate hand and breast hygiene).

Managing COVID-19 in Pregnancy

Pregnant people should be counseled about the increased risk for severe disease from SARS-CoV-2 and the measures they can take to protect themselves and their families from infection. These measures include practicing physical distancing, washing their hands regularly, and wearing a face covering (if indicated). If the patient is not vaccinated, they should be counseled about wearing a face covering and getting vaccinated against SARS-CoV-2 infection. CDC, the American College of Obstetricians and Gynecologists (ACOG), and the Society for Maternal-Fetal Medicine highlight the importance of accessing prenatal care. ACOG provides a list of frequently asked questions on using telehealth to

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deliver antenatal care, when appropriate.

ACOG has developed an algorithm to evaluate and manage pregnant outpatients with suspected or laboratory-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 that requires ICU admission. As in other patients, the illness severity, underlying comorbidities, and clinical status of pregnant patients with symptoms that are compatible with COVID-19 should 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 based on gestational age, when appropriate
- Individualized delivery planning
- A multispecialty, team-based approach that may include consultation with obstetric, maternal-fetal medicine, infectious disease, pulmonary-critical care, and pediatric specialists, as appropriate.

In general, the recommendations for managing COVID-19 in nonpregnant patients also apply to pregnant patients.

Therapeutic Management of COVID-19 in the Setting of Pregnancy

Potentially effective treatments for COVID-19 should not be withheld from pregnant people because of theoretical concerns related to the safety of using those therapeutic agents in pregnancy **(AIII)**.

Pregnant or lactating patients with COVID-19 and their clinical teams should discuss the use of investigational drugs or drugs that are approved for other indications as treatments for COVID-19. During this shared decision-making process, the patient and the clinical team should consider the safety of the medication for the pregnant or lactating individual and the fetus and the severity of maternal disease. For detailed guidance on the use of COVID-19 therapeutic agents during pregnancy, please refer to the pregnancy considerations subsections found in the Antiviral Therapy and Immunomodulators sections of these Guidelines.

The use of anti-SARS-CoV-2 monoclonal antibodies can be considered in pregnant people with COVID-19, especially in those who have additional risk factors for severe disease. There is no pregnancy-specific data on the use of monoclonal antibodies; however, other immunoglobulin G products have been safely used in pregnancy when their use is indicated. Therefore, these products should not be withheld in the setting of pregnancy.

To date, most SARS-CoV-2-related clinical trials have excluded individuals who are pregnant and lactating; in cases where lactating and pregnant individuals have been included in studies, only a small number have been enrolled. 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 and lactating individuals should not be excluded from clinical trials of therapeutic agents or vaccines for SARS-CoV-2 infection.

Timing of Delivery

ACOG provides detailed guidance on the timing of delivery and the risk of vertical transmission of SARS-CoV-2.

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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.

Post-Delivery

The majority of studies have not demonstrated the presence of SARS-CoV-2 in breast milk; therefore, breastfeeding is not contraindicated for people with laboratory-confirmed or suspected SARS-CoV-2 infection.[8] Precautions should be taken to avoid transmission to the infant, including practicing good hand hygiene, wearing face coverings, and performing proper pump cleaning before and after breast milk expression.

The decision to feed the infant breast milk while the patient is receiving therapeutic agents for COVID-19 should be a joint effort between the patient and the clinical team, including infant care providers. The patient and the clinical team should discuss the potential benefits of the therapeutic agent and evaluate the potential impact of pausing lactation on the future of breast milk delivery to the infant.

Specific guidance on the post-delivery management of infants born to mothers with known or suspected SARS-CoV-2 infection, including breastfeeding recommendations, is provided by CDC and the American Academy of Pediatrics, as well as the Special Considerations in Children section in these Guidelines.

SARS-CoV-2 Vaccine in Pregnancy

A study that used data from three vaccine safety reporting systems in the United States reported that the frequency of adverse events among 35,691 vaccine recipients who identified as pregnant was similar to the frequency observed among nonpregnant patients. Local injection site pain, nausea, and vomiting were reported slightly more frequently in pregnant people than in nonpregnant people. Other systemic reactions were reported more frequently among nonpregnant vaccine recipients, but the overall reactogenicity profile was similar for pregnant and nonpregnant patients. Surveillance data from 3,958 pregnant patients who were enrolled in CDC's v-safe Vaccine Pregnancy Registry showed that, among 827 people who completed their pregnancies, there were no obvious safety signals among obstetric or neonatal outcomes when rates of pregnancy loss (spontaneous abortion or stillbirth), preterm birth, congenital anomalies, infants who were small for gestational age, and neonatal death were compared to historic incidences in the peer-reviewed literature.[9] ACOG has published practice guidance on using COVID-19 vaccines in pregnant and lactating people, including a guide to assist clinicians during risk and benefit conversations with pregnant patients.

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Special Considerations in Children

Last Updated: February 24, 2022

Summary Recommendations

General Considerations
• SARS-CoV-2 infection is generally milder in children than in adults, and a substantial proportion of children with the disease have asymptomatic infection.
• Most children with SARS-CoV-2 infection will not require any specific therapy.
• Children who have a history of medical complexity (e.g., due to neurologic impairment, developmental delays, or genetic syndromes, including trisomy 21), obesity, chronic cardiopulmonary disease, or who are immunocompromised, as well as non-White children and older teenagers may be at increased risk for severe disease.
• There are limited data on the pathogenesis and clinical spectrum of COVID-19 disease in children. There are no pediatric data from placebo-controlled randomized clinical trials and limited data from observational studies to inform the development of pediatric-specific recommendations for the treatment of COVID-19.
 	
Specific Therapy for Children
• In the absence of adequate data on the treatment of children with acute COVID-19, recommendations are based on outcome and safety data for adult patients and the child's risk of disease progression.
• Most children with mild or moderate disease can be managed with supportive care alone **(AIII)**.
• **Remdesivir** is recommended for:
  • Hospitalized children aged ≥12 years with COVID-19 who have risk factors for severe disease and have an emergent or increasing need for supplemental oxygen **(BIII)**.
  • Hospitalized children aged ≥16 years with COVID-19 who have an emergent or increasing need for supplemental oxygen regardless of whether they have risks factors for severe disease **(BIII)**.
• In consultation with a pediatric infectious disease specialist, **remdesivir** can be considered for hospitalized children of all ages with COVID-19 who have an emergent or increasing need for supplemental oxygen **(CIII)**.
• The COVID-19 Treatment Guidelines Panel (the Panel) recommends using **dexamethasone** for hospitalized children with COVID-19 who require high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation **(BIII)**.
• There is insufficient pediatric evidence for the Panel to recommend either for or against the use of anti-SARS-CoV-2 monoclonal antibody products for children with COVID-19 who are not hospitalized but who have risk factors for severe disease. Based on adult studies, bamlanivimab plus etesevimab or casirivimab plus imdevimab may be considered on a case-by-case basis for nonhospitalized children who meet Emergency Use Authorization (EUA) criteria for high-risk of severe disease, especially those who meet more than 1 criterion or are aged ≥16 years. The Panel recommends consulting a pediatric infectious disease specialist in such cases.
• The Panel **recommends against** the use of **convalescent plasma** for hospitalized children with COVID-19 who do not require mechanical ventilation, except in a clinical trial **(AIII)**. The Panel **recommends against** the use of **convalescent plasma** for pediatric patients with COVID-19 who are mechanically ventilated **(AIII)**. In consultation with a pediatric infectious disease specialist, high-titer convalescent plasma may be considered on a case-by-case basis for hospitalized children who meet the EUA criteria for its use.
• There is insufficient evidence for the Panel to recommend either for or against the use of baricitinib in combination with remdesivir for the treatment of COVID-19 in hospitalized children in whom corticosteroids cannot be used.
• There is insufficient evidence for the Panel to recommend either for or against the use of tocilizumab in hospitalized children with COVID-19 or multisystem inflammatory syndrome in children (MIS-C). The Panel **recommends against** the use of **sarilumab** for hospitalized children with COVID-19 or MIS-C, except in a clinical trial **(AIII)**.
• MIS-C is a serious delayed complication of SARS-CoV-2 infection that may develop in a minority of children and young adults. See Therapeutic Management of Hospitalized Pediatric Patients With Multisystem Inflammatory Syndrome in Children (MIS-C) (With Discussion on Multisystem Inflammatory Syndrome in Adults [MIS-A]) for the Panel's recommendations for treating children with MIS-C.

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

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

Data from the Centers for Disease Control and Prevention (CDC) demonstrate a lower incidence of SARS-CoV-2 infection and severe disease in children than in adults.[1] However, without more systematic testing for children (including for children with mild symptoms as part of contact tracing) or seroprevalence studies, the true burden of pediatric SARS-CoV-2 infection remains unclear. Data on the pathogenesis and disease severity of SARS-CoV-2 infection in children are increasing but are still limited compared to the data in adults. Several large epidemiologic studies suggest that severe manifestations of acute disease are substantially less common in children than in adults. Although only a small percentage of children with COVID-19 will require medical attention, intensive care unit (ICU)-admission rates for hospitalized children are comparable to those for hospitalized adults with COVID-19.[2-10]

Clinical Manifestations

The signs and symptoms of SARS-CoV-2 infection in children may be similar to those in adults, but most children may be asymptomatic or only have a few symptoms. The most common signs and symptoms of COVID-19 in hospitalized children are fever, nausea/vomiting, cough, shortness of breath, and upper respiratory symptoms.[9,11] Of note, signs and symptoms of COVID-19 may overlap significantly with those of other viral infections, including influenza and other respiratory and enteric viral infections. Although the true incidence of asymptomatic SARS-CoV-2 infection is unknown, asymptomatic infection was reported in up to 45% of children who underwent surveillance testing at the time of hospitalization for a non-COVID-19 indication.[12]

SARS-CoV-2 has been associated with a potentially severe inflammatory syndrome in children and young adults (multisystem inflammatory syndrome in children [MIS-C]), which is discussed below.

Risk Factors

Data to clearly establish risk factors for severe COVID-19 in children are limited. Data reported to CDC show lower hospitalization rates and ICU admission rates for children with COVID-19 than for adults with the disease.[11,13] COVID-19-related hospitalization rates for children were highest in children aged <2 years and higher in Hispanic and Black children than in White children. The majority of hospitalized children with acute COVID-19 had underlying conditions, with obesity, chronic lung disease, and prematurity (data collected only for children aged <2 years) being the most prevalent.[14] Risk factors such as obesity may be more applicable to older teenagers.

In a large study of hospitalized children from the United Kingdom, age <1 month, age 10 to 14 years, and Black race were associated with admission to critical care units in a multivariate analysis.[9] Another large, multicenter study from Europe identified male sex, pre-existing medical conditions, and the presence of lower respiratory tract disease at presentation as additional risk factors for ICU admission in multivariable models.[10]

Deaths associated with COVID-19 among those aged <21 years are higher among children aged 10 to 20 years, especially young adults aged 18 to 20 years, as well as among Hispanic, Black, and American Indian/Alaska Native persons.[15] A high proportion of the fatal cases of pediatric COVID-19 are in children with underlying medical conditions, most commonly chronic lung disease, obesity, and neurological and developmental disorders.

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Based on data for adults with COVID-19 and extrapolations from data for non-COVID-19 pediatric respiratory viral infections, severely immunocompromised children and those with underlying cardiopulmonary disease may be at higher risk for severe COVID-19. Initial reports of SARS-CoV-2 infection among pediatric patients with cancer and pediatric solid organ transplant recipients have demonstrated a low frequency of infection and associated morbidity;[16-20] however, similar reports for other immunocompromised pediatric populations are limited.[21] A few reports have demonstrated a higher prevalence of asthma in pediatric COVID-19 cases, although the association between asthma and severe disease is not clearly defined.[7,8] Congenital heart disease may be associated with an increased risk of severe COVID-19, but the condition has not been consistently identified as a risk factor.[22,23] Guidance on the treatment of COVID-19 in children endorsed by the Pediatric Infectious Diseases Society specifies additional risk factors to consider when making decisions about antiviral and monoclonal antibody (mAb) therapy for pediatric patients.[24,25]

Persistent symptoms after acute COVID-19 have been described in adults, although the incidence of this sequelae in children remains unknown and is an active area of research (see Clinical Spectrum of SARS-CoV-2 Infection). Cardiac imaging studies have described myocardial injury in young athletes who had only mild disease;[26] additional studies are needed to determine long-term cardiac sequelae.

Vertical Transmission and Infants Born to People with SARS-CoV-2 Infection

Vertical transmission of SARS-CoV-2 is thought to be rare, but suspected or probable vertical transmission has been described.[27-29] Initial data on perinatal transmission of SARS-CoV-2 were limited to small case series with conflicting results; some studies demonstrated lack of transmission, whereas others were not able to definitively rule out this possibility.[30-33] Among 100 women with SARS-CoV-2 infection who delivered 101 infants, only 2 infants had equivocal reverse transcription polymerase chain reaction (RT-PCR) results that may have reflected SARS-CoV-2 infection, even though most of the infants remained with their mothers, in rooms with infection prevention measures in place, and were breast fed.[34]

Infants born to individuals with SARS-CoV-2 infection may have higher risk of poor clinical outcomes than those born to individuals without SARS-CoV-2 infection, although data are conflicting. In a systematic review of case series in pregnant women with confirmed SARS-CoV-2 infection (predominantly from China), the preterm birth rate was 20.1% (57 of 284 births were preterm; 95% CI, 15.8–25.1), the cesarean delivery rate was 84.7% (33 of 392 births were by cesarean delivery; 95% CI, 80.8–87.9), there was no vertical transmission, and the neonatal death rate was 0.3% (1 of 313 neonates died; 95% CI, 0.1–1.8).[35] In a prospective cohort study of 263 infants born in the United States, the rates for preterm births, neonatal ICU admissions, and respiratory disease did not differ between infants born to mothers with and without SARS-CoV-2 infection.[36] A cohort study from Sweden demonstrated that 5-minute Apgar scores and birth weight for gestational age did not differ between infants born to mothers with and without SARS-CoV-2 infection.[37] Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET) data from CDC that captured 598 hospitalized, pregnant women with SARS-CoV-2 infection showed a pregnancy loss rate of 2% among 458 pregnancies completed during COVID-19-related hospitalizations and a preterm birth rate of 12.9% compared to 10% for the general U.S. population.[38] A systematic review and meta-analysis of studies that included 2,567 pregnancies concluded that SARS-CoV-2-positive mothers were at increased risk of iatrogenic preterm birth. This risk was predominantly due to caesarean sections (21.8% of births) performed due to maternal illness and fear of maternal decompensation. In contrast, there was no increase in the rate of spontaneous preterm birth relative to the expected rate in pregnant individuals without SARS-CoV-2 infection.[39,40] Finally, a prospective cohort study from the United Kingdom of 66 neonates with SARS-CoV-2 infection found that 3% may have had vertically acquired infection

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and 12% had suspected nosocomially acquired infection.[29] Specific guidance on the diagnosis and management of COVID-19 in neonates born to people with known or suspected SARS-CoV-2 infection is provided by CDC.

Treatment Considerations

There are no results available from clinical trials that evaluated treatments for COVID-19 in children, and observational data on the safety or efficacy of drug therapy in children with COVID-19 are extremely limited. More high-quality studies, including randomized trials, are urgently needed. Guidance for the treatment of COVID-19 in children has been published and is mostly extrapolated from recommendations for adults with COVID-19.[41,42] The older the child and the more severe the disease, the more reasonable it is to follow recommendations for adult patients with COVID-19 (see Therapeutic Management of Nonhospitalized Adults With COVID-19 and Therapeutic Management of Hospitalized Adults With COVID-19). To address the uncertain safety and efficacy of these treatment options, children should be enrolled in clinical trials and multicenter pragmatic trials whenever possible.

The majority of children with mild or moderate COVID-19 will not progress to more severe illness and thus should be managed with supportive care alone **(AIII)**. The risks and benefits of therapy should be assessed based on illness severity, age, and the presence of the risk factors outlined above.

Remdesivir

Remdesivir is the only drug approved by the Food and Drug Administration (FDA) for the treatment of COVID-19 (see Remdesivir for more information). It is approved 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.[43] Remdesivir has not been evaluated in clinical trials that include children, and there have been no results from systematic evaluations of pharmacokinetics, efficacy, or toxicity in younger children, although studies are ongoing (see ClinicalTrials.gov). However, based on adult data, the potential benefits of remdesivir are likely to be greater for hospitalized children with COVID-19 who are at higher risk of progression due to older age (i.e., aged ≥16 years) or medical conditions than for those without these risk factors. **Remdesivir** is recommended for hospitalized children aged ≥12 years with COVID-19 who have risk factors for severe disease and have an emergent or increasing need for supplemental oxygen **(BIII)**. **Remdesivir** is also recommended for hospitalized children aged ≥16 years with COVID-19 who have an emergent or increasing need for supplemental oxygen even in the absence of risk factors **(BIII)**. **Remdesivir** can be considered for other hospitalized children of all ages with COVID-19 who have an emergent or increasing need for supplemental oxygen in consultation with a pediatric infectious disease specialist **(CIII)**.

Dexamethasone

Dexamethasone is recommended for the treatment of hospitalized adults with COVID-19 who require mechanical ventilation or supplemental oxygen through a high-flow device (see Corticosteroids and Therapeutic Management of Hospitalized Adults With COVID-19 for more information). The safety and effectiveness of dexamethasone or other corticosteroids for COVID-19 treatment have not been sufficiently evaluated in pediatric patients; thus, caution is warranted when extrapolating recommendations for adults to patients aged <18 years. The COVID-19 Treatment Guidelines Panel (the Panel) recommends using **dexamethasone** for children with COVID-19 who require high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) **(BIII)**. It is not routinely recommended for pediatric patients who require only low levels of oxygen support (i.e., via a nasal cannula only). Use of dexamethasone for the treatment of severe

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COVID-19 in children who are profoundly immunocompromised has not been evaluated, may be harmful, and therefore should be considered only on a case-by-case basis. If dexamethasone is not available, alternative glucocorticoids such as prednisone, methylprednisolone, or hydrocortisone can be considered. The dexamethasone dosing regimen for pediatric patients is dexamethasone 0.15 mg/kg/dose (maximum dose 6 mg) once daily for up to 10 days.

Anti-SARS-CoV-2 Monoclonal Antibodies

Although EUAs have been issued for bamlanivimab plus etesevimab, casirivimab plus imdevimab, and sotrovimab for the treatment of nonhospitalized, high-risk patients aged ≥12 years and weighing ≥40 kg with mild to moderate COVID-19, there are currently no data available to determine which high-risk pediatric patients defined in the EUAs will likely benefit from these therapies. Consequently, there is insufficient evidence for the Panel to recommend either for or against the use of these anti-SARS-CoV-2 mAbs in children with COVID-19 who are not hospitalized but are at high risk of severe disease and/or hospitalization. In consultation with a pediatric infectious disease specialist, anti-SARS-CoV-2 mAb can be considered on a case-by-case basis for children who meet the EUA criteria but should not be considered routine care. This recommendation is primarily based on the absence of data assessing the efficacy and safety in children and adolescents, limited data with which to identify children who are at the highest risk of severe COVID-19, the low overall risk of progression to serious disease in children, and the potential risk associated with infusion reactions.

Additional guidance is provided in a recent publication endorsed by the Pediatric Infectious Diseases Society.[25] There are currently no data to support the use of anti-SARS-CoV-2 mAbs in hospitalized children for COVID-19. Emerging data regarding the prevalence and clinical significance of SARS-CoV-2 variants, and the efficacy of mAbs against variants, may inform the choice of specific anti-SARS-CoV-2 mAb therapies in the future.

Convalescent Plasma

FDA has also issued an EUA for the use of high-titer convalescent plasma for the treatment of hospitalized patients with COVID-19 (see Convalescent Plasma for more information).[44] The safety and efficacy of convalescent plasma have not been evaluated in pediatric patients with COVID-19. There is insufficient evidence for the Panel to recommend either for or against the use of convalescent plasma for the treatment of COVID-19 in either pediatric outpatients or in hospitalized children who do not require mechanical ventilation. The Panel **recommends against** the use of **convalescent plasma** for pediatric patients with COVID-19 who are mechanically ventilated **(AIII)**. In consultation with a pediatric infectious disease specialist, convalescent plasma may be considered on a case-by-case basis for children who meet the EUA criteria for its use.

Baricitinib

FDA has also issued an 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, mechanical ventilation, or ECMO.[45] The safety and efficacy of baricitinib have not been evaluated in pediatric patients with COVID-19, and pediatric data regarding its use for other conditions are extremely limited. Thus, there is insufficient evidence for the Panel to recommend either for or against the use of baricitinib in combination with remdesivir for the treatment of COVID-19 in hospitalized children in whom corticosteroids cannot be used (see Kinase Inhibitors for more information).

Tocilizumab

Data on the use of tocilizumab for the treatment of non-COVID-19 conditions in children are limited to very specific clinical scenarios (e.g., chimeric antigen receptor T cell-related cytokine release

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syndrome).[46] The use of tocilizumab for severe cases of acute COVID-19 has been described in pediatric case series.[14,47] Data on tocilizumab efficacy from trials in adults with COVID-19 are conflicting, and benefit has only been demonstrated in a subset of hospitalized patients (see Interleukin-6 Inhibitors). There is insufficient evidence for the Panel to recommend either for or against the use of tocilizumab for hospitalized children with COVID-19 or MIS-C. If used, tocilizumab should be used in combination with dexamethasone. The Panel **recommends against** the use of **sarilumab** for hospitalized children with COVID-19 or MIS-C, except in a clinical trial **(AIII)**.

As for other agents outlined in these Guidelines, there is insufficient evidence for the Panel to recommend either for or against the use of specific antivirals or immunomodulatory agents for the treatment of COVID-19 in pediatric patients. Considerations such as underlying conditions, disease severity, and the potential for drug toxicity or drug interactions may inform decisions on the use of these agents in pediatric patients with COVID-19 on a case-by-case basis. Children should be enrolled in clinical trials that are evaluating COVID-19 therapies whenever possible. A number of additional drugs are being investigated for the treatment of COVID-19 in adults; refer to the Antiviral Therapy and Immunomodulators sections to review special considerations for using these drugs in children and refer to Table 2f and Table 4f for recommendations on pediatric dosing regimens.

Multisystem Inflammatory Syndrome in Children

A small subset of children and young adults with SARS-CoV-2 infection develop MIS-C. This immune manifestation is also referred to as pediatric multisystem inflammatory syndrome-temporally associated with SARS-CoV-2 (PMIS-TS), although the case definitions for the syndromes differ slightly. This syndrome was first described in Europe, where previously healthy children with severe inflammation and Kawasaki disease-like features were identified to have current or recent infection with SARS-CoV-2. The clinical spectrum of MIS-C has been described in the United States and is similar to that described for PMIS-TS. MIS-C is consistent with a post-infectious inflammatory syndrome related to SARS-CoV-2.[48,49] Most MIS-C patients have serologic evidence of previous SARS-CoV-2 infection, but only a minority are RT-PCR positive for SARS-CoV-2 at presentation.[50,51] The peak incidence of MIS-C lags about 4 weeks behind the peak of acute pediatric COVID-19 hospitalizations. Emerging data suggests that adults may also develop a similar syndrome, multisystem inflammatory syndrome in adults (MIS-A), although it is not clear if this is a postinfectious complication similar to MIS-C.[50-52] Although risk factors for MIS-C have not been established, in an analysis of MIS-C cases in the United States, most of the children were non-White, and obesity was the most common comorbidity.[53] Unlike in children with acute COVID-19, the majority of children who present with MIS-C do not seem to have underlying comorbid conditions other than obesity.

Clinical Manifestations

The current CDC case definition for MIS-C includes:

- An individual aged <21 years presenting with fever,[a] laboratory evidence of inflammation,[b] and evidence of clinically severe illness that requires hospitalization with multisystem (i.e., >2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological); *and*
- No alternative plausible diagnoses; *and*
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, antigen test, or serology results; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms.[54]

[a] Fever >38.0°C for ≥24 hours or report of subjective fever lasting ≥24 hours

[b] Including, but not limited to, 1 or more of the following: an elevated C-reactive protein, erythrocyte sedimentation rate,

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fibrinogen, procalcitonin, D-dimer, ferritin, lactate dehydrogenase, interleukin-6, or neutrophils, or reduced lymphocytes or albumin levels

Distinguishing MIS-C from other febrile illnesses in the community setting remains challenging, but the presence of persistent fever, multisystem manifestations, and laboratory abnormalities could help early recognition.[55] The clinical spectrum of hospitalized cases has included younger children with mucocutaneous manifestations that overlap with Kawasaki disease, older children with more multiorgan involvement and shock, and patients with respiratory manifestations that overlap with acute COVID-19. Patients with MIS-C are often critically ill, and up to 80% of children require ICU admission.[53] Most patients with MIS-C have markers of cardiac injury or dysfunction, including elevated levels of troponin and brain natriuretic protein.[50,51] Echocardiographic findings in these cases include impaired left ventricular function and coronary artery dilations, and, rarely, coronary artery aneurysms. The reported mortality rate in the United States for hospitalized children with MIS-C is 1% to 2%. Longitudinal studies are currently ongoing to examine the long-term sequelae of MIS-C.

The pathogenesis of MIS-C is still being elucidated. Differences have been demonstrated between MIS-C and typical Kawasaki disease in terms of epidemiology, cytopenias, cytokine expression, and elevation of inflammatory markers. Immunologic profiling has also shown differences in cytokine expression (tumor necrosis factor alpha and interleukin-10) between MIS-C and acute COVID-19 in children.[56-58]

Management

Please see Therapeutic Management of Hospitalized Pediatric Patients With Multisystem Inflammatory Syndrome in Children (MIS-C) (With Discussion on Multisystem Inflammatory Syndrome in Adults [MIS-A]) for the Panel's recommendations for treating MIS-C in children.

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Special Considerations in Adults and Children With Cancer

Last Updated: May 31, 2022

Summary Recommendations
• COVID-19 vaccination remains the most effective way to prevent SARS-CoV-2 infection and should be considered the first line of prevention. The COVID-19 Treatment Guidelines Panel (the Panel) recommends COVID-19 vaccination as soon as possible for everyone who is eligible **(AI)**, including patients with active cancer and patients who are receiving treatment for cancer **(AIII)**. • Because vaccine response rates may be lower in people with cancer, specific guidance on administering vaccines to these individuals is provided by the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices. The Panel recommends following the most current COVID-19 vaccination schedule for people with cancer. • Vaccinating household members, close contacts, and health care providers who provide care to patients with cancer is important to protect these patients from infection. All close contacts are strongly encouraged to get vaccinated against COVID-19 as soon as possible **(AIII)**. • Patients with cancer are at high risk of progressing to serious COVID-19, and they may be eligible to receive anti-SARS-CoV-2 monoclonal antibodies as pre-exposure prophylaxis (PrEP). • The Panel recommends performing diagnostic molecular or antigen testing for SARS-CoV-2 in patients with cancer who develop signs and symptoms that suggest acute COVID-19 **(AIII)**. The Panel also recommends performing diagnostic molecular testing 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 Therapeutic Management of Nonhospitalized Adults With COVID-19 and Therapeutic Management of Hospitalized Adults With COVID-19 for more information. • Clinicians should pay careful attention to potential overlapping toxicities and drug-drug interactions between drugs that are used to treat COVID-19 (e.g., ritonavir-boosted nirmatrelvir [Paxlovid], dexamethasone) and cancer-directed therapies, prophylactic antimicrobials, and other medications **(AIII)**. • Clinicians who are treating COVID-19 in patients with cancer should consult a hematologist or oncologist before adjusting cancer-directed medications **(AIII)**. • 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)**.
Rating of Recommendations: A = Strong; B = Moderate; C = Weak **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 clinical outcomes of COVID-19 are generally worse in people with cancer than in people 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] A patient's risk of immunosuppression and susceptibility to SARS-CoV-2 infection depend on the type of cancer, the treatments administered, and the stage of disease (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, patients with cancer who were in remission or who had no evidence of disease had a lower risk of death from COVID-19 than those who were receiving active treatment.[6] It is unclear whether cancer survivors have an increased risk for severe COVID-19 and its complications compared to people without a history of cancer.

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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 testing for SARS-CoV-2, managing COVID-19 in patients with cancer, and managing 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.

COVID-19 Vaccination in Patients With Cancer

The clinical trials that evaluated the COVID-19 vaccines that have received Emergency Use Authorizations (EUAs) and/or approvals from the Food and Drug Administration (FDA) excluded severely immunocompromised patients. The Center for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices notes that the COVID-19 vaccines that are authorized for use in the United States are not live vaccines; therefore, they can be safely administered to immunocompromised people.[7] Given the effectiveness of the COVID-19 vaccines in the general population and the increased risk of severe COVID-19 and mortality in patients with cancer, the COVID-19 Treatment Guidelines Panel (the Panel) recommends COVID-19 vaccination for patients with active cancer and patients who are receiving treatment for cancer **(AIII)**. Observational data suggest that the serological responses to vaccines may be blunted in immunocompromised patients; however, vaccination is still recommended for these patients, because it may provide partial protection, including protection from vaccine-induced, cell-mediated immunity.[8,9] See the CDC website COVID-19 Vaccines for People who are Moderately or Severely Immunocompromised for the current COVID-19 vaccination schedule for these individuals. Given the effectiveness of COVID-19 vaccines, the Panel recommends COVID-19 vaccination as soon as possible for everyone who is eligible **(AI)**, including individuals who have immunodeficiency or are on immunosuppressive medications **(AIII)**.

Vaccinating household members, close contacts, and health care providers who provide care to patients with cancer is important to protect these patients from infection. All close contacts are strongly encouraged to get vaccinated as soon as possible **(AIII)**. There is evidence that vaccinated individuals who are infected with SARS-CoV-2 have lower viral loads than unvaccinated individuals[10,11] and that COVID-19 vaccines reduce the incidence of SARS-CoV-2 infections not only among vaccinated individuals but also among their household contacts.[12-14]

The mRNA vaccines contain polyethylene glycol (PEG), and the Johnson & Johnson (J&J)/Janssen vaccine contains polysorbate. For patients who experience severe anaphylactic reactions to PEG-asparaginase, consider performing allergy testing for PEG prior to vaccination with either of the mRNA vaccines, or consider using the J&J/Janssen vaccine with precautions.[15-17]

When determining the timing of COVID-19 vaccination in patients with cancer, clinicians should consider the following factors:

- If possible, patients who are planning to receive chemotherapy should complete vaccination for

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COVID-19 at least 2 weeks before starting chemotherapy.[18,19]

- In patients with hematologic malignancy who are undergoing intensive chemotherapy (e.g., induction chemotherapy for acute myelogenous leukemia), vaccination should be delayed until neutrophil recovery.[20]
- Hematopoietic stem cell and chimeric antigen receptor T cell recipients can be offered COVID-19 vaccination starting at least 3 months after therapy.[19,20]

It is unknown whether the immune response to COVID-19 vaccination can increase the risk of graft-versus-host disease. No immune-related adverse events were reported after COVID-19 vaccination in two studies of patients with cancer who received immune checkpoint inhibitors.[21,22]

Decreased immunologic responses to COVID-19 vaccination have been reported in patients who were receiving treatment for solid tumors and hematologic malignancies.[9,23] The type of therapy has been shown to influence the patient's response to vaccination. For example, people with chronic lymphocytic leukemia who were treated with Bruton's tyrosine kinase inhibitors or venetoclax with or without anti-CD20 antibodies had extremely low response rates (16.0% and 13.6%, respectively).[23] In comparison, approximately 80% to 95% of patients with solid tumors showed immunologic responses.[9,24,25] Several observational studies support the use of a third vaccine dose in patients with cancer, even though vaccine failure may still occur.[26-28] See the CDC website COVID-19 Vaccines for People who are Moderately or Severely Immunocompromised for guidance on vaccine dosing.

Pre-Exposure Prophylaxis

Vaccination remains the most effective way to prevent SARS-CoV-2 infection and should be considered the first line of prevention. However, some individuals, including some patients with cancer, cannot or may not mount an adequate protective response to COVID-19 vaccines. These patients are at high risk of progressing to severe COVID-19 and may be eligible to receive the anti-SARS-CoV-2 monoclonal antibodies tixagevimab plus cilgavimab (Evusheld) as pre-exposure prophylaxis (PrEP). See Prevention of SARS-CoV-2 Infection for more information.

Testing for SARS-CoV-2 in Patients With Cancer

The Panel recommends performing diagnostic molecular or antigen testing for SARS-CoV-2 in patients with cancer who develop signs and symptoms that suggest acute 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 patient's risk of developing neutropenia.[29] A retrospective study suggests that patients with cancer and neutropenia have a higher mortality rate if they develop COVID-19.[30] Studies have reported an increased risk of poor clinical outcomes for patients with COVID-19 in the setting of neutropenia and/or during the perioperative period.[31,32] Because of this, the Panel recommends performing diagnostic molecular testing for SARS-CoV-2 in asymptomatic patients prior to procedures that require anesthesia and before initiating cytotoxic chemotherapy and long-acting biologic therapy **(BIII)**.

General Guidance on Medical Care for Patients With Cancer 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. Telemedicine may improve access to providers for medically or socially vulnerable populations, but it could worsen disparities if these

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populations have limited access to technology. Nosocomial transmission of SARS-CoV-2 to patients and health care workers has been reported.[33-35] Health care providers and patients should take precautions to reduce the risk of SARS-CoV-2 exposure and infection, including wearing a mask, maintaining a distance of 6 feet from others, and practicing good hand hygiene.[36]

Decisions about treatment regimens, surgery, and radiation therapy for the underlying malignancy should be made on a case-by-case basis, and clinicians should consider the biology of the cancer, the need for hospitalization, the number of clinic visits required, and the anticipated degree of immunosuppression. Additional factors that should be considered include the following:

- If possible, avoid treatment delays 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.[37]
- The potential risks of drug-related lung toxicity (e.g., from using bleomycin or PD-1 inhibitors) must be balanced with the clinical efficacy of alternative regimens or the risk of delaying care.[38]
- Preventing neutropenia can decrease the risk of neutropenic fever and the need for emergency department evaluation and hospitalization. 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.[39]
- Cancer treatment regimens that do not affect the outcomes of COVID-19 in patients with cancer 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 patients with cancer and COVID-19.[40]
- Radiation therapy guidelines suggest increasing the dose per fraction and reducing the number of daily treatments to minimize the number of hospital visits.[41,42]

Blood supply shortages will likely continue during the COVID-19 pandemic due to social distancing, cancellation of blood drives, and infection among donors. The FDA has proposed revising the donor criteria to increase the number of eligible donors.[43] In patients with cancer, stricter transfusion thresholds for blood products (e.g., red blood cells, platelets) in asymptomatic patients should be considered. At this time, there is no evidence that COVID-19 can be transmitted through blood products.[44]

Febrile Neutropenia

Patients with cancer and febrile neutropenia should undergo diagnostic molecular or antigen testing for SARS-CoV-2 and evaluation for other infectious agents. They should also be given empiric antibiotics, as outlined in the NCCN Guidelines.[45] 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.[45] 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.[46,47]

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The recommendations for treating COVID-19 in patients with cancer are the same as those for the general population **(AIII)**. See Therapeutic Management of Nonhospitalized Adults With COVID-19 and Therapeutic Management of Hospitalized Adults With COVID-19 for more information. Patients with cancer are at high risk of progressing to severe COVID-19, and they may be eligible to receive anti-SARS-CoV-2 therapies in the outpatient setting if they develop mild to moderate COVID-19.

The use of dexamethasone has been associated with a lower mortality rate in patients with COVID-19 who require supplemental oxygen or mechanical ventilation.[48] In patients with cancer, 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 dexamethasone are expected to be the same in patients with cancer as in those 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.

Tocilizumab or baricitinib used in combination with dexamethasone is recommended for some patients with severe or critical COVID-19 who exhibit rapid respiratory decompensation (see Therapeutic Management of Hospitalized Adults With COVID-19).[49-51] The risks and benefits of using dexamethasone in combination with tocilizumab or baricitinib in patients with cancer who recently received chemotherapy is unknown. Because dexamethasone, tocilizumab, and baricitinib are immunosuppressive agents, patients who receive these medications should be closely monitored for secondary infections.

Therapeutic anticoagulation for patients with cancer who are hospitalized for COVID-19 should be managed similarly to anticoagulation for other hospitalized patients. Patients with platelet counts <50,000 cells/μL should not receive therapeutic anticoagulation to treat COVID-19. Clinicians should follow hospital protocols for managing anticoagulation in patients with thrombocytopenia.

The NCCN recommends against using G-CSF and granulocyte-macrophage colony-stimulating factor in patients with cancer and acute COVID-19 who do not have bacterial or fungal infections to avoid the hypothetical risk of increasing inflammatory cytokine levels and pulmonary inflammation.[52,53] Secondary infections (e.g., invasive pulmonary aspergillosis) have been reported in critically ill patients with COVID-19.[54,55]

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 time to initiate or restart cancer-directed therapies after the infection has resolved is unclear. If possible, clinicians should withhold treatment until COVID-19 symptoms have resolved. Prolonged viral shedding may occur in patients with cancer,[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. Clinicians who are treating COVID-19 in patients with cancer should consult a hematologist or oncologist before adjusting cancer-directed medications **(AIII)**.

Medication Interactions

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

A 5-day course of ritonavir-boosted nirmatrelvir (Paxlovid) is 1 of the preferred therapies for treating

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mild to moderate COVID-19 in nonhospitalized patients who are at risk for disease progression. However, this regimen has the potential for significant and complex drug-drug interactions with concomitant medications, primarily due to the ritonavir component of the combination. Boosting with ritonavir, a strong cytochrome P450 (CYP) 3A inhibitor, is required to increase the exposure of nirmatrelvir to a concentration that is effective against SARS-CoV-2. Ritonavir may also increase concentrations of certain concomitant medications, including certain chemotherapeutic agents and immunotherapies that are used to treat cancer. Significant increases in the concentrations of these drugs may lead to serious and sometimes life-threatening drug toxicities. Additionally, ritonavir is an inhibitor, inducer, and substrate of various other drug-metabolizing enzymes and/or drug transporters.

Before prescribing ritonavir-boosted nirmatrelvir, clinicians should carefully review the patient's concomitant medications. Clinicians should refer to resources such as the Liverpool COVID-19 Drug Interactions website, Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications, and the FDA EUA fact sheet for ritonavir-boosted nirmatrelvir for guidance on identifying and managing potential drug-drug interactions. If significant interactions prohibit the concomitant use of ritonavir-boosted nirmatrelvir, another COVID-19 treatment option should be used.

Dexamethasone is commonly used as an antiemetic for patients with cancer and is recommended for the treatment of certain patients with COVID-19 (see Therapeutic Management of Hospitalized Adults With COVID-19). Dexamethasone is a weak to moderate CYP3A4 inducer; therefore, interactions with any CYP3A4 substrates need to be considered.

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.[56-58] Guidance on managing children with cancer during the COVID-19 pandemic is available from an international group that received input from the International Society of Paediatric Oncology, the Children's Oncology Group, St. Jude Global, and Childhood Cancer International.[59] Two publications provide guidance on managing specific malignancies and supportive care and a summary of web links from groups of experts that are relevant to the care of pediatric oncology patients during the COVID-19 pandemic.[59,60] Special considerations for using antiviral drugs in immunocompromised children, including those with malignancy, are available in a multicenter guidance statement.[61]

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

Last Updated: May 31, 2022

Summary Recommendations

Vaccination for COVID-19

- COVID-19 vaccination remains the most effective way to prevent SARS-CoV-2 infection and should be considered the first line of prevention. Given the effectiveness of COVID-19 vaccines in the general population and the increased risk of worse clinical outcomes of COVID-19 in transplant and cellular immunotherapy candidates and recipients, the COVID-19 Treatment Guidelines Panel (the Panel) recommends COVID-19 vaccination for these patients **(AIII)**.
- Because vaccine response rates may be lower in moderately or severely immunocompromised patients, specific guidance on administering vaccines to these individuals is provided by the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices. The Panel recommends following the current COVID-19 vaccination schedule for these patients.
- Vaccinating household members, close contacts, and health care providers who provide care to transplant and cellular immunotherapy candidates and recipients is important to protect these patients from infection. All close contacts are strongly encouraged to get vaccinated against COVID-19 as soon as possible **(AIII)**.
- All potential organ and stem cell donors are encouraged to get vaccinated against COVID-19 **(AI)**.

Pre-Exposure Prophylaxis

- Some transplant candidates or recipients cannot or may not mount an adequate protective response to COVID-19 vaccines. These patients are eligible to receive the anti-SARS-CoV-2 monoclonal antibodies tixagevimab plus cilgavimab (Evusheld) as pre-exposure prophylaxis (PrEP). See Prevention of SARS-CoV-2 Infection for more information.

Potential Transplant and Cellular Immunotherapy Candidates

- The Panel recommends performing diagnostic molecular or antigen testing for SARS-CoV-2 for all potential solid organ transplant, hematopoietic stem cell transplant (HCT), and cellular immunotherapy candidates with signs and symptoms that suggest acute COVID-19 **(AIII)**.
- The Panel recommends following the guidance from medical professional organizations that specialize in providing care for solid organ transplant, HCT, or cellular immunotherapy recipients when performing diagnostic molecular or antigen 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)**.
- 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 candidates are the same as those for nontransplant candidates **(AIII)**.

Potential Transplant Donors

- The Panel recommends assessing all potential solid organ transplant and HCT donors for signs and symptoms of COVID-19 according to guidance from medical professional organizations **(AIII)**.
  - The Panel recommends performing diagnostic molecular or antigen 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)**.

Transplant and Cellular Immunotherapy Recipients With COVID-19

- Clinicians should follow the guidelines for evaluating and managing COVID-19 in nontransplant patients when treating transplant and cellular immunotherapy recipients **(AIII)**. See Therapeutic Management of Hospitalized Adults With COVID-19 and Therapeutic Management of Nonhospitalized Adults With COVID-19 for more information.
- Immunocompromised patients with mild to moderate COVID-19 are at high risk of progressing to severe disease and should receive anti-SARS-CoV-2 therapies for treatment.

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Summary Recommendations, continued
• Clinicians who are treating COVID-19 in transplant and cellular immunotherapy patients should consult a transplant specialist before adjusting immunosuppressive medications **(AIII)**. • When treating COVID-19, clinicians should pay careful attention to potential overlapping toxicities and drug-drug interactions between drugs that are used to treat COVID-19 (e.g., ritonavir-boosted nirmatrelvir [Paxlovid]) and immunosuppressants, prophylactic antimicrobials, or other medications **(AIII)**.
Rating of Recommendations: A = Strong; B = Moderate; C = Weak **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, hematopoietic stem cell transplant (HCT), and cellular immunotherapy recipients can be challenging due to the presence of coexisting medical conditions, the potential for transplant-related cytopenias, and the need for chronic immunosuppressive therapy to prevent graft rejection and graft-versus-host disease. Transplant recipients may also have a higher risk of exposure to 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 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 impact of transplantation on disease severity difficult to assess.

The International Society for Heart and Lung Transplantation, the American Society of Transplantation (AST), the American Society for Transplantation and Cellular Therapy (ASTCT), and the European Society for Blood and Marrow Transplantation (EBMT) provide guidance for clinicians who are caring for transplant recipients with COVID-19 and guidance on screening potential donors and transplant or cellular immunotherapy candidates. In addition, the American Society of Hematology offers guidance regarding COVID-19 vaccination for transplant and cellular immunotherapy recipients. This section of the COVID-19 Treatment Guidelines complements these sources and focuses on considerations for managing COVID-19 in solid organ transplant, HCT, and cellular immunotherapy 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 those for nontransplant patients **(AIII)**. See Therapeutic Management of Hospitalized Adults With COVID-19 and Therapeutic Management of Nonhospitalized Adults With COVID-19 for more information. The risks and benefits of each medication that is used to treat COVID-19 may be different for transplant patients and nontransplant patients.

COVID-19 Vaccination in Solid Organ Transplant, Hematopoietic Stem Cell Transplant, and Cellular Immunotherapy Candidates, Donors, and Recipients

The clinical trials that evaluated the safety and efficacy of the COVID-19 vaccines excluded severely immunocompromised patients.[1-3] The Center for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices notes that the currently authorized or approved COVID-19 vaccines are not live vaccines; therefore, they can be safely administered to immunocompromised people.[4] However, solid organ transplant recipients have reduced immunological antibody responses following a primary 2-dose or 3-dose series of the mRNA COVID-19 vaccines.[5-8]

Given the effectiveness of COVID-19 vaccines in the general population and the increased risk of worse

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clinical outcomes of COVID-19 in transplant and cellular immunotherapy recipients, the COVID-19 Treatment Guidelines Panel (the Panel) recommends COVID-19 vaccination for potential transplant and cellular immunotherapy candidates and recipients **(AIII)**. See the CDC website COVID-19 Vaccines for People Who Are Moderately or Severely Immunocompromised for the current COVID-19 vaccination schedule for all populations, including transplant and cellular immunotherapy recipients.

When determining the timing of COVID-19 vaccination in solid organ transplant, HCT, and cellular immunotherapy recipients, clinicians should consider the following factors:

- Ideally, solid organ transplant candidates should receive COVID-19 vaccines while they are awaiting transplant.
- In general, vaccination should be completed at least 2 weeks prior to a solid organ transplant or started 1 month after a solid organ transplant.
- In certain situations, it may be appropriate to delay vaccination until 3 months after a solid organ transplant, such as when T cell- or B cell-ablative therapy (with antithymocyte globulin or rituximab) is used at the time of transplant.[9]
- At this time, reducing the dose of immunosuppressants and withholding immunosuppressants prior to vaccination **are not recommended**.
- COVID-19 vaccines can be offered as early as 3 months after a patient receives HCT or chimeric antigen receptor T cell therapy, although the efficacy of the vaccines may be reduced compared to the efficacy observed in the general population.[10-12] Patients who are scheduled to receive cytotoxic or B cell-depleting therapies should complete their COVID-19 vaccination prior to initiation or between cycles of cytotoxic or B cell-depleting therapies, if possible.
- After completing COVID-19 vaccination, immunocompromised persons should be advised to continue to exercise precautions to reduce their risk of SARS-CoV-2 exposure and infection (e.g., they should wear a mask, maintain a distance of 6 feet from others, and avoid crowds and poorly ventilated spaces).[13]

There is insufficient evidence for the Panel to recommend either for or against the use of SARS-CoV-2 serologic testing to assess for immunity or to guide clinical decisions about using COVID-19 vaccines. It is currently unknown whether revaccination offers a clinical benefit for people who received COVID-19 vaccines during treatment with immunosuppressive drugs.

Vaccinating household members, close contacts, and health care providers who provide care to transplant and cellular immunotherapy candidates and recipients is important to protect these patients from infection. All close contacts are strongly encouraged to get vaccinated against COVID-19 as soon as possible **(AIII)**. There is evidence that vaccinated individuals who are infected with SARS-CoV-2 have lower viral loads than unvaccinated individuals[14,15] and that COVID-19 vaccines reduce the incidence of SARS-CoV-2 infections not only among vaccinated individuals but also among their household contacts.[16-18] All potential organ and stem cell donors are encouraged to get vaccinated against COVID-19 **(AI)**.

Pre-Exposure Prophylaxis

Vaccination remains the most effective way to prevent SARS-CoV-2 infection and should be considered the first line of prevention. However, some individuals, including some transplant candidates and recipients, cannot or may not mount an adequate protective response to COVID-19 vaccines. These patients are at high risk of progressing to severe COVID-19 and may be eligible to receive the anti-SARS-CoV-2 monoclonal antibodies (mAbs) tixagevimab plus cilgavimab (Evusheld) as pre-exposure

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prophylaxis (PrEP). See Prevention of SARS-CoV-2 Infection for more information.

Assessing SARS-CoV-2 Infection in Transplant and Cellular Immunotherapy Candidates and Donors

The risk of transmission of SARS-CoV-2 from donors to candidates is unknown. The probability that a donor or candidate may have SARS-CoV-2 infection can be estimated by considering the epidemiologic risk, obtaining a clinical history, and testing with molecular techniques. No current testing strategy is sensitive enough or specific enough to totally exclude active infection.

Assessing Transplant and Cellular Immunotherapy Candidates

The Panel recommends performing diagnostic molecular or antigen testing for SARS-CoV-2 for all potential solid organ transplant candidates with signs and symptoms that suggest acute COVID-19 **(AIII)**. All potential solid organ transplant 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 a solid organ transplant **(AIII)**.

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

Assessing Donors

Living solid organ donors should be counseled on strategies to prevent infection and be monitored for exposures and symptoms in the 14 days prior to a scheduled transplant.19 Living donors should undergo SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) testing with a sample collected from the respiratory tract within 3 days of donation. Deceased donors should be tested for SARS-CoV-2 infection using an RT-PCR assay of a sample taken from the upper respiratory tract within 72 hours of death; ideally, the test should be performed as close to organ recovery as possible. Deceased donors can be considered for donation if the results are negative. Lower respiratory sampling for COVID-19 testing is required for potential lung transplant donors by the United Network for Organ Sharing.[20]

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)**. HCT donors should practice good hygiene and avoid crowded places and large gatherings during the 28 days prior to donation.[21] Recommendations for screening HCT donors 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 solid organ transplant candidate, transplant should be deferred, if possible. The optimal disease-free interval before transplantation is not known. When deciding on the appropriate timing for the transplant, clinicians should consider both the risk of viral transmission and the risks to the candidate if the transplant is deferred, such as the potential progression of the underlying disease and the risk of death. This decision should be continually reassessed as conditions evolve.

Donors for solid organ transplants who test positive for SARS-CoV-2 are medically ineligible for donation.[22] Current guidelines recommend deferring transplants or immunotherapy procedures, including peripheral blood stem cell mobilization, bone marrow harvest, T cell collection, and conditioning/ lymphodepletion, in HCT and cellular immunotherapy candidates who test positive for SARS-CoV-2 or who have clinical symptoms that are consistent with infection. Final decisions should be made on a

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case-by-case basis while weighing the risks of delaying or altering therapy for the underlying disease.

Transplant Recipients With COVID-19

Solid organ transplant recipients who are receiving immunosuppressive therapy should be considered to be at increased risk for severe COVID-19.[23,24] A national survey of 88 U.S. transplant centers conducted between March 24 and 31, 2020, reported that 148 solid organ transplant recipients received a diagnosis of SARS-CoV-2 infection (69.6% were kidney recipients, 15.5% were liver recipients, 8.8% were heart recipients, and 6.1% were lung recipients).[25] COVID-19 was mild in 54% of recipients and moderate in 21% of recipients, and 25% of recipients were critically ill. Initial reports of transplant recipients who were hospitalized with COVID-19 suggest mortality rates of up to 28%.[26-30]

Risk of Graft Rejection

There are concerns that COVID-19 itself may increase the risk for acute rejection. Acute cellular rejection should not be presumed in solid organ transplant recipients without biopsy confirmation, regardless of whether the individual has COVID-19. Similarly, immunosuppressive therapy should be initiated in recipients with or without COVID-19 who have rejection confirmed by a biopsy.[23]

There are limited data on the incidence and clinical characteristics of SARS-CoV-2 infection in HCT[31] and cellular immunotherapy recipients.[32] Recent data from the Center for International Blood and Marrow Transplant Research demonstrated a mortality rate of approximately 30% within a month of COVID-19 diagnosis among a cohort of 318 HCT recipients.[33] This mortality rate was observed in both allogeneic and autologous recipients. Older age (≥50 years), male sex, and receipt of a COVID-19 diagnosis within 12 months of transplantation were associated with a higher risk of mortality among allogeneic recipients. In autologous recipients, patients with lymphoma had a higher risk of mortality than patients who had plasma cell disorder or myeloma.

A smaller study demonstrated a slightly lower mortality rate among HCT and cellular immunotherapy recipients than earlier reports. This study found that the number of comorbidities, the presence of infiltrates on initial chest imaging, and neutropenia were predictors for increased disease severity.[34] Additional factors that have been used to determine the clinical severity of other respiratory viral infections include the degree of cytopenia, the intensity of the conditioning regimen, the graft source, the degree of mismatch, and the need for further immunosuppression to manage graft-versus-host disease. Prolonged viral shedding has been described in solid organ transplant and HCT recipients; this can have implications for preventing infection and for the timing of therapeutic interventions.[35]

Treating COVID-19 in Transplant Recipients

Currently, remdesivir is the only antiviral drug that is approved by the Food and Drug Administration for the treatment of COVID-19 in both nonhospitalized and hospitalized patients. Outpatient transplant recipients who are immunosuppressed or who have certain underlying comorbidities are candidates for several other therapeutic agents that are available through Emergency Use Authorizations (EUAs). See Therapeutic Management of Nonhospitalized Adults With COVID-19 for more information.

When treating hospitalized patients with mild to moderate, symptomatic COVID-19, clinicians should consider administering the therapeutics used in nonhospitalized patients with similar disease severity. Data from a large randomized controlled trial found that a short course of dexamethasone (6 mg once daily for up to 10 days) improved survival in hospitalized people with severe COVID-19 who were mechanically ventilated or who required supplemental oxygen.[36] Tocilizumab or baricitinib used in combination with dexamethasone is recommended for some patients with severe or critical COVID-19 who exhibit rapid respiratory decompensation (see Therapeutic Management of Hospitalized Adults

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With COVID-19).[36-38] Because dexamethasone, tocilizumab, and baricitinib are immunosuppressive agents, patients who receive these medications should be closely monitored for secondary infections.

Therapeutic anticoagulation for transplant recipients who are hospitalized for COVID-19 should be managed similarly to anticoagulation for other hospitalized patients. Patients with platelet counts <50,000 cells/μL should not receive therapeutic anticoagulation to treat COVID-19. Clinicians should follow hospital protocols for managing anticoagulation in patients with thrombocytopenia.

The Panel's recommendations for the use of remdesivir, dexamethasone, tocilizumab, baricitinib, and anticoagulation in hospitalized patients with COVID-19 can be found in Therapeutic Management of Hospitalized Adults With COVID-19.

Concomitant Medications

Clinicians should pay special attention to the potential for drug-drug interactions and overlapping toxicities between treatments for COVID-19 and concomitant medications, such as immunosuppressants that are used to prevent allograft rejection, 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.[27] Clinicians who are treating COVID-19 in transplant patients should consult a transplant specialist before adjusting immunosuppressive medications **(AIII)**.

Drug-Drug Interactions

Calcineurin inhibitors (e.g., cyclosporine, tacrolimus) and mammalian target of rapamycin (mTOR) inhibitors (e.g., everolimus, sirolimus), which are commonly used to prevent allograft rejection, have a narrow therapeutic index. Medications that inhibit or induce cytochrome P450 (CYP) enzymes or P-glycoprotein may put patients who receive these drugs 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.[39]

A 5-day course of ritonavir-boosted nirmatrelvir (Paxlovid) is 1 of the preferred therapies for treating mild to moderate COVID-19 in nonhospitalized patients who are at risk for disease progression. However, this regimen has the potential for significant and complex drug-drug interactions with concomitant medications, primarily due to the ritonavir component of the combination. Boosting with ritonavir, a strong CYP3A inhibitor, is required to increase the exposure of nirmatrelvir to a concentration that is effective against SARS-CoV-2. Ritonavir may also increase concentrations of certain concomitant medications, including calcineurin and mTOR inhibitors, during the treatment course and for ≥3 days after ritonavir is discontinued. Significant increases in the concentrations of these drugs may lead to serious and sometimes life-threatening drug toxicities.

For nonhospitalized transplant patients who are receiving calcineurin or mTOR inhibitors as part of their antirejection regimen, AST recommends either an anti-SARS-CoV-2 mAb or remdesivir as the first-line therapy.[40] If these drugs are not available or feasible to use, ritonavir-boosted nirmatrelvir may be used with caution. Ritonavir-boosted nirmatrelvir should only be used when close monitoring of the patient is possible, and clinicians should consult with transplant specialists during the treatment course. General guidance for coadministering ritonavir-boosted nirmatrelvir with concomitant medications includes temporarily withholding certain immunosuppressive agents (e.g., tacrolimus, everolimus, sirolimus) or reducing the dosage of certain immunosuppressive agents (e.g., cyclosporine), monitoring the patient closely for toxicities, and performing therapeutic drug monitoring (if possible) during and after the

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treatment course of ritonavir-boosted nirmatrelvir.[40,41]

Some small case series have reported real-life success in using these recommendations to manage patients;[42,43] however, cases of significant toxicities due to supratherapeutic tacrolimus concentrations have also been reported.[44] The reintroduction or dose modification of calcineurin and mTOR inhibitors in patients who have completed a course of ritonavir-boosted nirmatrelvir should be guided by therapeutic drug monitoring. Clinicians should also consult with a specialist who has experience with dose management. Clinicians should take additional precautions when treating transplant recipients who are also receiving other concomitant medications (e.g., certain triazole antifungals) that may interact with ritonavir, the immunosuppressants, or both. The extent and significance of multiple drug-drug interactions are much more complex and unpredictable.

Clinicians should refer to resources such as the Liverpool COVID-19 Drug Interactions website, Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications, and the EUA fact sheet for ritonavir-boosted nirmatrelvir for guidance on identifying and managing potential drug-drug interactions. If significant interactions prohibit the concomitant use of ritonavir-boosted nirmatrelvir, another COVID-19 treatment option should be used.

Among the drugs that are commonly used to treat hospitalized patients with COVID-19, dexamethasone is a moderate inducer of CYP3A4, and interleukin-6 inhibitors may lead to increased metabolism of CYP substrates. Clinicians should closely monitor the serum concentrations of calcineurin and mTOR inhibitors when these drugs are used.

Additional details about the adverse effects and drug-drug interactions of antiviral medications, anti-SARS-CoV-2 antibody products, and immune-based therapies for COVID-19 are noted in Tables 2f, 3c, and 4f.

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Special Considerations in People With HIV

Last Updated: May 2, 2022

Summary Recommendations
Prevention of COVID-19 • The COVID-19 Treatment Guidelines Panel (the Panel) recommends that people with HIV receive COVID-19 vaccines regardless of their CD4 T lymphocyte (CD4) cell count or HIV viral load, because the potential benefits outweigh the potential risks **(AIII)**. • The Advisory Committee on Immunization Practices recommends that people with advanced or untreated HIV who received a 2-dose series of an mRNA COVID-19 vaccine should receive a third dose of that vaccine at least 28 days after the second dose. Advanced HIV is defined as people with CD4 counts <200 cells/mm^3, a history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV. • People with advanced or untreated HIV who do not have SARS-CoV-2 infection and who have not been recently exposed to SARS-CoV-2 are eligible to receive the anti-SARS-CoV-2 monoclonal antibodies (mAbs) tixagevimab plus cilgavimab as pre-exposure prophylaxis (PrEP). See Prevention of SARS-CoV-2 Infection for details. • Two anti-SARS-CoV-2 mAb combinations, **bamlanivimab plus etesevimab** and **casirivimab plus imdevimab**, have received Emergency Use Authorizations from the Food and Drug Administration for post-exposure prophylaxis (PEP). However, the Panel **recommends against** their use in patients with COVID-19, including in people with HIV, because the Omicron variant is currently the dominant SARS-CoV-2 variant in the United States, and it is not susceptible to these anti-SARS-CoV-2 mAbs **(AIII)**. **Diagnosis of COVID-19** • The Panel recommends using the same approach for diagnosing SARS-CoV-2 infection in people with 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 generally the same as those for the general population **(AIII)**. • Nonhospitalized people with HIV and mild to moderate COVID-19 may be eligible to receive anti-SARS-CoV-2 therapy (e.g., ritonavir-boosted nirmatrelvir [Paxlovid], bebtelovimab, remdesivir, molnupiravir). However, in situations where there are logistical or supply constraints for administering these drugs, priority should be given to those with very advanced HIV (e.g., those with CD4 counts <50 cells/mm^3) **(AIII)**. See the Panel's statement on patient prioritization for outpatient therapies for details. • People with HIV who are taking ritonavir-based or cobicistat-based antiretroviral therapy (ART) can receive ritonavir-boosted nirmatrelvir to treat COVID-19 without altering or interrupting their ART (i.e., they can continue using the ritonavir or cobicistat dose that is associated with their ART in addition to the dose of ritonavir that is used with nirmatrelvir). • In people with advanced HIV and suspected or documented COVID-19, HIV-associated opportunistic infections should also be considered in the differential diagnosis of febrile illness **(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, antiretroviral (ARV) medications, antimicrobial therapies, and other medications **(AIII)**. • People with HIV should be offered the opportunity to participate in clinical trials that are evaluating agents for the prevention and treatment of SARS-CoV-2 infection. **Management of HIV** • People with HIV who develop COVID-19, including those who require hospitalization, should continue their ART and opportunistic infection treatment and prophylaxis whenever possible **(AIII)**. • Clinicians who are treating COVID-19 in people with HIV should consult an HIV specialist before adjusting or switching ARV medications **(AIII)**. • An ARV regimen should not be switched or adjusted (i.e., by adding ARV drugs to the regimen) for the purpose of preventing or treating SARS-CoV-2 infection **(AIII)**.

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Summary Recommendations, continued
• Clinicians should consult an HIV specialist to determine the optimal time to initiate ART in people who present with COVID-19 and a new diagnosis of HIV.
Rating of Recommendations: A = Strong; B = Moderate; C = Weak **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 people in the United States are living with 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 people of lower socioeconomic status in the United States;[2] these demographic groups also appear to have a higher risk of poor outcomes with COVID-19. In the general population, the individuals who are at the highest risk of severe COVID-19 include those aged >60 years; those who are pregnant; those who have received solid organ transplants; and those with comorbidities, such as cancer, obesity, diabetes mellitus, cardiovascular disease, pulmonary disease, a history of smoking, chronic kidney disease, or chronic liver disease.[3] Many people with HIV have 1 or more comorbidities that may put them at increased risk for a more severe course of COVID-19.

Information on SARS-CoV-2/HIV coinfection is evolving rapidly. The sections below outline the current state of knowledge regarding preventing and diagnosing SARS-CoV-2 infection in people with HIV, the treatment and clinical outcomes in people with HIV who develop COVID-19, and the management of HIV during the COVID-19 pandemic. In addition to these Guidelines, the Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents has developed the Guidance for COVID-19 and People With HIV.

Clinical Outcomes of COVID-19 in People With HIV

Data are emerging on the clinical outcomes of COVID-19 in people with HIV. In some of the initial case series of people with COVID-19 in Europe and the United States, no significant differences were observed in the clinical outcomes of COVID-19 between people with HIV and people who did not have HIV.[4-11]

In contrast, more recent reports suggest worse outcomes for patients with HIV and COVID-19, including increased COVID-19 mortality rates in cohort studies in the United States, the United Kingdom, and South Africa.[12-18] HIV was independently associated with an increased risk of severe and critical COVID-19 in a large World Health Organization platform trial that included data from 24 countries.[19] In a multicenter cohort study of 286 patients with HIV and COVID-19 in the United States, lower CD4 T lymphocyte (CD4) cell counts (i.e., <200 cells/mm^3) were associated with a higher risk for the composite endpoint of intensive care unit admission, mechanical ventilation, or death. This increased risk was observed even in patients who had achieved virologic suppression of HIV.[15] In a large observational cohort study of people with HIV and COVID-19 in the United States, those with CD4 counts <350 cells/mm^3 were more likely to be hospitalized, require ventilation, or die. Higher levels of viremia were also associated with worse outcomes.[18] In another study of 175 patients with HIV and COVID-19, a low CD4 count or a low CD4 nadir was associated with poor outcomes.[16] In a cohort study conducted in New York, people with HIV and COVID-19 had higher rates of hospitalization and mortality than people with COVID-19 who did not have HIV.[17]

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Prevention of COVID-19 in People With HIV

The COVID-19 Treatment Guidelines Panel (the Panel) recommends using the same approach for advising persons with HIV on the strategies to prevent SARS-CoV-2 infection that is used for people without HIV **(AIII)**. There is currently no clear evidence that any antiretroviral (ARV) medications can prevent SARS-CoV-2 infection.

People with HIV should receive COVID-19 vaccines, regardless of their CD4 count or HIV viral load, because the potential benefits outweigh the potential risks **(AIII)**. People with HIV were included in the clinical trials of the 2 mRNA vaccines and the adenovirus vector vaccine that are currently available through Emergency Use Authorizations (EUAs) and/or approval from the Food and Drug Administration (FDA);[20-22] however, few studies have evaluated the safety and efficacy of these vaccines in people with HIV. Typically, people with HIV who are on ART and who have achieved virologic suppression respond well to licensed vaccines. Preliminary data from studies that used COVID-19 vaccines in people with HIV confirm that people who are on ART and have normal CD4 counts have good immunologic responses to the vaccines.[23-25]

On August 12, 2021, the FDA changed the EUAs for the 2 mRNA vaccines to allow a third dose of an mRNA vaccine to be administered at least 28 days after the second dose to people with advanced or untreated HIV. Advanced HIV is defined as people with CD4 counts <200 cells/mm^3, a history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV. People with HIV should also receive booster doses of the COVID-19 vaccines as recommended by the Advisory Committee on Immunization Practices.

People with advanced or untreated HIV who are not infected or recently exposed to SARS-CoV-2 are eligible to receive the anti-SARS-CoV-2 monoclonal antibodies (mAbs) tixagevimab plus cilgavimab as pre-exposure prophylaxis (PrEP). See Prevention of SARS-CoV-2 Infection for details.

Two anti-SARS-CoV-2 mAb combinations, **bamlanivimab plus etesevimab** and **casirivimab plus imdevimab,** have received FDA EUAs for post-exposure prophylaxis (PEP). However, the Panel **recommends against** their use in patients with COVID-19, including in people with HIV, because the Omicron variant is currently the dominant variant in the United States, and it is not susceptible to these anti-SARS-CoV-2 mAbs **(AIII)**.

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 diagnosing SARS-CoV-2 infection in people with HIV as in those without HIV **(AIII)**. See Testing for SARS-CoV-2 Infection for more information. There is currently no evidence that the performance characteristics of nucleic acid amplification tests (NAATs) and antigen tests differ in people with and without HIV when diagnosing acute SARS-CoV-2 infection. The Panel **recommends against** the use of serologic testing as the sole basis for diagnosis of acute SARS-CoV-2 infection **(AIII)**. However, if diagnostic serologic testing is performed in a patient with HIV, the results should be interpreted with caution because cross-reactivity between antibodies to SARS-CoV-2 and HIV has been reported.[26]

Correlation of CD4 Count in People With HIV and COVID-19

The normal range for CD4 counts in healthy adults is about 500 to 1,600 cells/mm^3. People with HIV who have a CD4 count of ≥500 cells/mm^3 have similar cellular immune function to those 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 polymerase

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chain reaction 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 people with advanced HIV who have presented with COVID-19 and another coinfection, including *Pneumocystis jirovecii* pneumonia.[27,28] In patients with advanced HIV who have suspected or laboratory-confirmed SARS-CoV-2 infection, clinicians should consider a broader differential diagnosis for clinical symptoms and consider consulting an HIV specialist **(AIII)**.

Clinical Presentation of COVID-19 in People With HIV

It is currently unknown whether people with HIV have a higher incidence of SARS-CoV-2 infection or a higher rate of progression to symptomatic disease than the general population. Approximately 50% of people with HIV in the United States are aged >50 years,[29] and many have comorbidities that are associated with more severe cases of COVID-19. These comorbidities include hypertension, diabetes mellitus, cardiovascular disease, a history of smoking, chronic lung disease, chronic liver disease, and cancer.[30]

There are a number of case reports and case series that describe the clinical presentation of COVID-19 in people with HIV.[4-11,31,32] These studies indicate that the clinical presentation of COVID-19 is similar in people with and without HIV. Most of the published reports describe populations in which most of the individuals with HIV are on ART and have achieved virologic suppression. Consequently, the current understanding of the impact of COVID-19 in those with advanced HIV who have low CD4 counts or 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 for those without HIV **(AIII)**. Nonhospitalized people with HIV and mild to moderate COVID-19 may be eligible to receive the therapies that are currently recommended for treatment (see Therapeutic Management of Nonhospitalized Adults With COVID-19). However, in situations where there are logistical or supply constraints for administering these therapies, priority should be given to those with advanced 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)**. Therapeutic options for nonhospitalized patients with HIV include ritonavir-boosted nirmatrelvir (Paxlovid), intravenous remdesivir, bebtelovimab, and molnupiravir (see Therapeutic Management of Nonhospitalized Adults With COVID-19). Drug-drug interactions are a special concern with ritonavir-boosted nirmatrelvir (see the Panel's statement on the drug-drug interactions for ritonavir-boosted nirmatrelvir). People with HIV who are taking ritonavir-based or cobicistat-based ART can receive the 5-day course of ritonavir-boosted nirmatrelvir to treat COVID-19 without altering or interrupting their ART (i.e., they can continue using the ritonavir or cobicistat dose that is associated with their ART in addition to the dose of ritonavir that is used with nirmatrelvir). Before prescribing ritonavir-boosted nirmatrelvir for a patient who is not already on a ritonavir-based or cobicistat-based regimen, clinicians should carefully review the patient's concomitant medications, including over-the-counter medicines and herbal supplements, and evaluate the potential for drug-drug interactions. Clinicians should utilize resources such as the EUA fact sheet for ritonavir-boosted nirmatrelvir and the Liverpool COVID-19 Drug Interactions website for additional

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guidance on identifying and managing drug-drug interactions.

In hospitalized patients, the appropriate treatment strategy depends on disease severity (see Therapeutic Management of Hospitalized Adults With COVID-19). Both tocilizumab and dexamethasone, which are recommended for some patients with severe or critical COVID-19, are immunosuppressive agents. The safety of using these drugs in immunocompromised patients, including those with advanced HIV, has not been studied. Therefore, patients with advanced HIV who are receiving these drugs should be closely monitored for secondary infections. Dexamethasone is a dose-dependent inducer of cytochrome P450 3A4 and could potentially lower the levels of certain coadministered ARV drugs. More than a single dose of dexamethasone **is not recommended** for patients who are receiving rilpivirine as part of their ARV regimen. Clinicians should consult an HIV specialist before administering dexamethasone to these patients. It is currently unknown whether administering ≤10 days of dexamethasone impacts the clinical efficacy of other ARV drugs. Patients with HIV who are receiving dexamethasone as treatment for COVID-19 should follow up with their HIV providers to assess their virologic response.

Although some ARV drugs were 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. The data on whether these medications are safe to use in patients with HIV are lacking. If a medication has been shown 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.

Managing HIV in People With COVID-19

Whenever possible, ART and opportunistic infection prophylaxis should be continued in a patient with HIV who develops COVID-19, including in those who require hospitalization **(AIII)**. Treatment interruption may lead to rebound viremia, and, in some cases, the emergence of drug resistance. If the appropriate ARV drugs are not on the hospital's formulary, administer medications from the patient's home supplies, if available.

Clinicians who are treating COVID-19 in people with HIV should consult an HIV specialist before adjusting or switching a patient's ARV medications. An ARV regimen should not be switched or adjusted (i.e., by adding ARV drugs 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, tenofovir disoproxil fumarate/emtricitabine), have been or are being evaluated in clinical trials or are prescribed off-label to treat or prevent SARS-CoV-2 infection. To date, lopinavir/ritonavir and darunavir/cobicistat have not been found to be effective (see Lopinavir/Ritonavir and Other HIV Protease Inhibitors).[33,34] Two retrospective studies have suggested that tenofovir disoproxil fumarate/emtricitabine may play a role in preventing SARS-CoV-2 acquisition or hospitalization or death associated with COVID-19; however, the significance of these findings is unclear, as neither study adequately controlled for confounding variables such as age and comorbidities.[12,32]

For patients who are taking an investigational ARV medication as part of their ARV 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 ARV pills may be crushed. Clinicians should consult an HIV specialist and/or pharmacist to assess the best way to continue an effective ARV regimen for a patient with a feeding tube. Information may be available in the drug product label or in this document from Toronto General

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Hospital.

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 consulting an HIV specialist about initiating or reinitiating ART as soon as clinically feasible. If ART is initiated, maintaining treatment and linking patients to HIV care upon hospital discharge is critical. If an HIV specialist is not available, clinical consultation is available by phone through the National Clinician Consultation Center, Monday through Friday, 9 am to 8 pm EST.

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Influenza and COVID-19

Last Updated: October 27, 2021

Summary Recommendations

Influenza Vaccination
• People with acute COVID-19 should receive an inactivated influenza vaccine **(BIII)**. For more information on administering influenza vaccines to these patients, see Interim Guidance for Routine and Influenza Immunization Services During the COVID-19 Pandemic from the Centers for Disease Control and Prevention (CDC).
  • Clinicians should consider deferring influenza vaccination for symptomatic COVID-19 patients until these patients have completed their COVID-19 isolation period and are no longer moderately or severely ill.
  • People with SARS-CoV-2 infection who are not moderately or severely ill (including those who are asymptomatic) should seek influenza vaccination when they no longer require isolation. They can be vaccinated sooner if they are in a health care setting for other reasons.
• An influenza vaccine and a COVID-19 vaccine may be administered concurrently at different injection sites (see the recommendations from CDC and the Advisory Committee on Immunization Practices).
Diagnosis of Influenza and COVID-19 When Influenza Viruses and SARS-CoV-2 Are Cocirculating
• Only testing can distinguish between SARS-CoV-2 and influenza virus infections and identify SARS-CoV-2 and influenza virus coinfection.
• The COVID-19 Treatment Guidelines Panel (the Panel) recommends testing for both viruses in all hospitalized patients with acute respiratory illness **(AIII)**.
• The Panel recommends influenza testing in addition to SARS-CoV-2 testing in outpatients with acute respiratory illness if the results will change the clinical management strategy for the patient (e.g., administering antiviral treatment for influenza) **(BIII)**.
• Clinicians should consider testing patients for other pathogens based on their specific clinical circumstances. Additional testing is especially important for patients with influenza who have a high risk of acquiring bacterial superinfections.
• 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
• Antiviral treatment of influenza is the same in all patients with or without SARS-CoV-2 coinfection **(AIII)**.
  • For information on using antiviral drugs to treat influenza in hospitalized and nonhospitalized patients, see the CDC and IDSA recommendations.
• The Panel recommends that hospitalized patients with suspected influenza be started on empiric treatment for influenza with oseltamivir **as soon as possible** and without waiting for influenza test results **(AIIb)**.
• Antiviral treatment for influenza can be stopped when influenza has been ruled out by the results of a nucleic acid detection assay in upper respiratory tract specimens for nonintubated patients and in both upper and lower respiratory tract specimens for intubated patients.

Rating of Recommendations: A = Strong; B = Moderate; C = Weak **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 2021 to 2022 influenza season is difficult to predict, and activity may vary depending on location and the measures taken by individual communities to mitigate the spread of SARS-CoV-2.[1] Influenza activity worldwide has been very low since the early spring of 2020, including in the United States during the 2020 to 2021 season.[2,3] Clinicians should monitor local influenza and SARS-CoV-2 activities during influenza season to inform the evaluation and management

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of patients with acute respiratory illness. This can be done by tracking local and state public health surveillance data, assessing the results of testing performed at health care facilities, and reviewing the Centers for Disease Control and Prevention (CDC) Weekly U.S. Influenza Surveillance Report.

Influenza Vaccination

For Patients With Acute COVID-19 or Those Who Are Recovering From COVID-19

The Advisory Committee on Immunization Practices (ACIP) recommends offering an influenza vaccine to all persons aged ≥6 months in the United States by the end of October.[4] People with acute COVID-19 should receive an inactivated influenza vaccine **(BIII)**.

There are currently no available data on the safety, immunogenicity, or efficacy 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.[5] Clinicians should consider deferring influenza vaccination for symptomatic COVID-19 patients until these patients have completed their COVID-19 isolation period and are no longer moderately or severely ill. People with SARS-CoV-2 infection who are not moderately or severely ill (including those who are asymptomatic) should seek influenza vaccination when they no longer require isolation. They can be vaccinated sooner if they are in a health care setting for other reasons (see Interim Guidance for Routine and Influenza Immunization Services During the COVID-19 Pandemic from CDC for more detailed recommendations).

It is not known whether administering dexamethasone or other immunomodulatory therapies to patients with severe COVID-19 will affect the immune response to an influenza vaccine. Nevertheless, as long as influenza viruses are circulating, people with COVID-19 should receive an influenza vaccine once they have substantially improved or recovered from COVID-19. See the influenza vaccine recommendations from CDC, ACIP, and the American Academy of Pediatrics.

Coadministration of COVID-19 Vaccines and Influenza Vaccines

Although there are currently no data on the coadministration of COVID-19 vaccines and influenza vaccines, these vaccines may be administered concurrently at different injection sites. Providers and patients should be aware of the potential for increased reactogenicity when administering both vaccines concurrently (see the recommendations from CDC and ACIP).

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 is needed to distinguish between SARS-CoV-2 and influenza virus and to identify coinfection in people with an acute respiratory illness. Coinfection with influenza and SARS-CoV-2 has been described in case reports and case series.[6-10]

Testing 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 who are hospitalized with an acute respiratory

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illness (see Testing for SARS-CoV-2 Infection) **(AIII)**. SARS-CoV-2 testing should also be performed in outpatients with suspected COVID-19, and influenza testing can be considered if the results will change the clinical management strategy for the patient (e.g., administering antiviral treatment for influenza) **(BIII)**. Several multiplex molecular assays and multiplex antigen assays that detect SARS-CoV-2 and influenza A and B viruses have received Food and Drug Administration Emergency Use Authorizations or De Novo classifications and can provide results in 15 minutes to 8 hours using a single respiratory specimen.[11,12] For more information, see the CDC Information for Clinicians on Influenza Virus Testing and the recommendations from the Infectious Diseases Society of America (IDSA) on the use of influenza tests and the interpretation of testing results.[13]

Treating Influenza With Antiviral Agents

Antiviral treatment for influenza is the same for all patients regardless of SARS-CoV-2 coinfection **(AIII)**. 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** and without waiting for influenza testing results **(AIIb)**. Oseltamivir has no activity against SARS-CoV-2[14] or known interactions with remdesivir or other therapeutics for COVID-19. The standard dose of 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.[13] There are no data on peramivir activity against SARS-CoV-2. See the CDC Influenza Antiviral Medications: Summary for Clinicians for clinical algorithms for using antiviral agents in patients with suspected or laboratory-confirmed influenza, including pregnant people and other people who are at high risk for influenza complications. The IDSA Clinical Practice Guidelines also provide recommendations on using antiviral agents to treat influenza, and the American Academy of Pediatrics provides recommendations on the antiviral treatment of influenza in children.

When the result of an influenza nucleic acid detection assay from an upper respiratory tract specimen is negative in a patient who is receiving antiviral treatment for influenza:

- *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 using an influenza nucleic acid detection assay. If the lower respiratory tract specimen is also negative, influenza antiviral treatment can be stopped.

COVID-19 Treatment Considerations for Hospitalized Patients With Suspected or Confirmed Influenza Virus Coinfection

- Corticosteroids, which are used for the treatment of patients with severe COVID-19, may prolong influenza viral replication and viral RNA detection and may be associated with poor outcomes for influenza.[13,15] Currently, no data are available on the use of corticosteroids in patients with SARS-CoV-2 and influenza virus coinfection. However, because dexamethasone has demonstrated substantial benefits for patients with COVID-19 who require supplemental oxygen, the benefits of using corticosteroids in patients with severe SARS-CoV-2 and influenza virus coinfection likely outweigh any potential harms.
- Remdesivir does not have activity against influenza viruses. There are no known drug interactions between remdesivir and oseltamivir. Therefore, remdesivir may be used safely when indicated in patients with COVID-19 and suspected or laboratory-confirmed influenza who are receiving oseltamivir treatment.

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- Although severe influenza may be associated with a dysregulated innate immune response, there are no data on the use of immunomodulatory therapies, such as interleukin-6 inhibitors (e.g., tocilizumab, sarilumab) or Janus Kinase inhibitors (e.g., baricitinib, tofacitinib), for the treatment of severe influenza. There are also no data on the effect these therapies may have on influenza viral replication. Because these immunomodulators have demonstrated a clinical benefit in certain COVID-19 patients, clinicians should consider engaging in a shared decision-making process on use of these drugs with patients who have been diagnosed with COVID-19 and who have suspected or laboratory-confirmed influenza.
- The co-occurrence of community-acquired secondary bacterial pneumonia and COVID-19 appears to be infrequent and may be more common in people who also have influenza; however, this inference is based on limited data.[16-18] 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*.[13]
- Patients with COVID-19 who develop new respiratory symptoms with or without fever or respiratory distress and who do not have 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 24, 2022

Name	Affiliation
Co-Chairs	
Roy M. Gulick, MD, MPH	Weill Cornell Medicine, New York, NY
H. Clifford Lane, MD	National Institutes of Health, Bethesda, MD
Henry Masur, MD	National Institutes of Health, Bethesda, MD
Executive Secretary	
Alice K. Pau, PharmD	National Institutes of Health, Bethesda, MD
Members	
Judith Aberg, MD	Icahn School of Medicine at Mount Sinai, New York, NY
Adaora Adimora, MD, MPH	University of North Carolina School of Medicine, Chapel Hill, NC
Jason Baker, MD, MS	Hennepin Healthcare/University of Minnesota, Minneapolis, MN
Lisa Baumann Kreuziger, MD, MS	Versiti/Medical College of Wisconsin, Milwaukee, WI
Roger Bedimo, MD, MS	University of Texas Southwestern/Veterans Affairs North Texas Health Care System, Dallas, TX
Pamela S. Belperio, PharmD	Department of Veterans Affairs, Los Angeles, CA
Stephen V. Cantrill, MD	Denver Health, Denver, CO
Kathleen Chiotos, MD, MSCE	Children's Hospital of Philadelphia/University of Pennsylvania, Philadelphia, PA
Craig Coopersmith, MD	Emory University School of Medicine, Atlanta, GA
Eric Daar, MD	Harbor-UCLA Medical Center, Torrance, CA
Amy L. Dzierba, PharmD	New York-Presbyterian Hospital, New York, NY
Gregory Eschenauer, PharmD	University of Michigan, Ann Arbor, MI
Laura Evans, MD, MSc	University of Washington, Seattle, WA
John J. Gallagher, DNP, RN	University of Pittsburgh Medical Center, Pittsburgh, PA
Rajesh Gandhi, MD	Massachusetts General Hospital/Harvard Medical School, Boston, MA
David V. Glidden, PhD	University of California San Francisco, San Francisco, CA
Steve Grapentine, PharmD	University of California San Francisco, San Francisco, CA
Birgit Grund, PhD	University of Minnesota, Minneapolis, MN
Erica J. Hardy, MD, MMSc	Warren Alpert Medical School of Brown University, Providence, RI
Carl Hinkson, MSRC	Providence Health & Services, Everett, WA
Lauren Henderson, MD, MMSc	Boston Children's Hospital/Harvard Medical School, Boston, MA
Brenna L. Hughes, MD, MSc	Duke University School of Medicine, Durham, NC
Steven Johnson, MD	University of Colorado School of Medicine, Aurora, CO
Marla J. Keller, MD	Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY
Robinder Khemani, MD, MsCI	Children's Hospital of Los Angeles/University of Southern California, Los Angeles, CA
Arthur Kim, MD	Massachusetts General Hospital/Harvard Medical School, Boston, MA
Jeffrey L. Lennox, MD	Emory University School of Medicine, Atlanta, GA
Mitchell M. Levy, MD	Warren Alpert Medical School of Brown University, Providence, RI
Jonathan Li, MD, MMSc	Brigham and Women's Hospital/Harvard Medical School, Boston, MA
Gregory Martin, MD, MSc	Emory University School of Medicine, Atlanta, GA
Susanna Naggie, MD, MHS	Duke University School of Medicine, Durham, NC

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Name	Affiliation
Members, continued	
Andrew T. Pavia, MD	University of Utah School of Medicine, Salt Lake City, UT
Grant Schulert, MD, PhD	Cincinnati Children's Hospital Medical Center/University of Cincinnati College of Medicine, Cincinnati, OH
Nitin Seam, MD	National Institutes of Health, Bethesda, MD
Steven Q. Simpson, MD	University of Kansas Medical Center, Kansas City, KS
Renee Stapleton, MD, PhD	University of Vermont Larner College of Medicine, Burlington, VT
Susan Swindells, MBBS	University of Nebraska Medical Center, Omaha, NE
Pablo Tebas, MD	University of Pennsylvania, Philadelphia, PA
Phyllis Tien, MD, MSc	University of California, San Francisco/San Francisco VA Healthcare System, San Francisco, CA
Alpana A. Waghmare, MD	Seattle Children's Hospital, Seattle, WA
Jinoos Yazdany, MD, MPH	University of California, San Francisco, San Francisco, CA
Community Members	
Danielle M. Campbell, MPH	University of California, Los Angeles, Los Angeles, CA
Carly Harrison	LupusChat, New York, NY
Pharmacology Consultants	
Sarita Boyd, PharmD	Food and Drug Administration, Silver Spring, MD
Jomy George, PharmD	National Institutes of Health, Bethesda, MD
Kimberly Scarsi, PharmD	University of Nebraska Medical Center, Omaha, NE
Ex Officio Members, U.S. Government Representatives	
Timothy Burgess, MD	Department of Defense, Bethesda, MD
Demetre Daskalakis, MD, MPH	Centers for Disease Control and Prevention, Atlanta, GA
Derek Eisnor, MD	Biomedical Advanced Research and Development Authority, Washington, DC
Joseph Francis, MD, MPH	Department of Veterans Affairs, Washington, DC
Virginia Sheikh, MD, MHS	Food and Drug Administration, Silver Spring, MD
Timothy M. Uyeki, MD, MPH	Centers for Disease Control and Prevention, Atlanta, GA
U.S. Government Support Team	
John T. Brooks, MD	Centers for Disease Control and Prevention, Atlanta, GA
Richard T. Davey, Jr., MD	National Institutes of Health, Bethesda, MD
Laurie K. Doepel, BA	National Institutes of Health, Bethesda, MD
Alison Han, MD (Co-Team Coordinator)	National Institutes of Health, Bethesda, MD
Elizabeth S. Higgs, MD, DTM&H, MIA	National Institutes of Health, Bethesda, MD
Martha C. Nason, PhD (Biostatistics Support)	National Institutes of Health, Bethesda, MD
Michael Proschan, PhD (Biostatistics Support)	National Institutes of Health, Bethesda, MD
Renee Ridzon, MD	National Institutes of Health, Bethesda, MD
Kanal Singh, MD, MPH (Co-Team Coordinator)	National Institutes of Health, Bethesda, MD
Assistant Executive Secretaries	
Page Crew, PharmD, MPH	National Institutes of Health, Bethesda, MD
Safia Kuriakose, PharmD	Frederick National Laboratory for Cancer Research, in support of NIAID, Frederick, MD
Andrea M. Lerner, MD, MS	National Institutes of Health, Bethesda, MD

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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: April 29, 2022

Reporting Period: April 1, 2021, to March 31, 2022

Panel Member	Financial Disclosure	
	Company	**Relationship**
Judith Aberg, MD	Atea Pharmaceuticals	Research Support
	Emergent BioSolutions	Research Support
	Gilead Sciences	Research Support
	GlaxoSmithKline	Advisory Board, Research Support
	GSK/ViiV Healthcare	Advisory Board, Research Support
	Janssen	Research Support
	Merck & Co.	Advisory Board, Research Support
	Pfizer	Research Support
	Regeneron	Research Support
Adaora Adimora, MD, MPH	Gilead Sciences	Research Support, Consultant
	Merck & Co.	Advisory Board, Research Support
Jason Baker, MD, MS	Humanigen	Research Support
Lisa Baumann Kreuziger, MD, MS	3M	Stockholder, Spouse is employee
	Versiti	Employee
Roger Bedimo, MD, MS	Gilead Sciences	Advisory Board
	GSK/ViiV Healthcare	Advisory Board
	Janssen	Advisory Board
	Merck & Co.	Advisory Board, Research Support
Pamela S. Belperio, PharmD	None	N/A
John T. Brooks, MD	None	N/A
Timothy Burgess, MD	AstraZeneca	Research Support
Danielle M. Campbell, MPH	Gilead Sciences	Advisory Board
	GSK/ViiV Healthcare	Attendee (Community Stakeholder Meeting)
Stephen V. Cantrill, MD	None	N/A
Kathleen Chiotos, MD, MSCE	None	N/A
Craig Coopersmith, MD	None	N/A
Page Crew, PharmD, MPH	None	N/A
Eric Daar, MD	Gilead Sciences	Consultant, Research Support
	GSK/ViiV Healthcare	Consultant, Research Support
	Merck & Co.	Consultant, Research Support
Demetre Daskalakis, MD, MPH	None	N/A
Richard T. Davey, Jr., MD	None	N/A
Laurie K. Doepel, BA	None	N/A
Amy L. Dzierba, PharmD	None	N/A
Derek Eisnor, MD	None	N/A

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Panel Member	Financial Disclosure	
	Company	Relationship
Gregory Eschenauer, PharmD	None	N/A
Laura Evans, MD, MSc	None	N/A
Joseph Francis, MD, MPH	None	N/A
John J. Gallagher, DNP, RN	None	N/A
Rajesh Gandhi, MD	None	N/A
David V. Glidden, PhD	None	N/A
Steve Grapentine, PharmD	None	N/A
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, Consultant
	Aurinia Pharmaceuticals	Advisory Board, Stockholder
	UCB	Advisory Board, Consultant
Lauren Henderson, MD, MMSc	Adaptive Biotechnologies	Consultant
	Bristol Myers Squibb	Research Support
	Pfizer	External Panel (Grant Reviews)
	Sobi	Advisory Board, Consultant, Research Support
Elizabeth S. Higgs, MD, DTM&H, MIA	None	N/A
Carl Hinkson, MSRC	None	N/A
Brenna L. Hughes, MD, MSc	None	N/A
Steven Johnson, MD	GSK/ViiV Healthcare	Advisory Board
Marla J. Keller, MD	None	N/A
Robinder Khemani, MD, MsCI	None	N/A
Arthur Kim, MD	Kintor Pharmaceutical	Data and Safety Monitoring Board Chair/Member
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	None	N/A
Jonathan Li, MD, MMSc	None	N/A
Gregory Martin, MD, MSc	Genentech	Data and Safety Monitoring Board Chair/Member
	Grifols	Research Grants Review Panel
Henry Masur, MD	None	N/A
Susanna Naggie, MD, MHS	AbbVie	Research Support, Funding via NIH supported trial
	Bristol Myers Squibb	Event Adjudication Committee
	FHI 360	Event Adjudication Committee
	Gilead Sciences	Research Support
	Pardes Biosciences	Consultant
	Silverback Therapeutics	Consultant
	Vir Biotechnology	Advisory Board, Stockholder, Stock Options

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Panel Member	Financial Disclosure	
	Company	Relationship
Martha C. Nason, PhD	None	N/A
Alice K. Pau, PharmD	None	N/A
Andrew T. Pavia, MD	GlaxoSmithKline	Advisory Board
Michael Proschan, PhD	None	N/A
Renee Ridzon, MD	None	N/A
Grant Schulert, MD, PhD	Novartis	Honoraria
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
Renee Stapleton, MD, PhD	Altimmune	Data and Safety Monitoring Board Chair
	CSL Behring	Consultant
Susan Swindells, MBBS	GSK/ViiV Healthcare	Research Support
Pablo Tebas, MD	Gilead Sciences	Consultant
	GSK/ViiV Healthcare	Consultant
	Merck & Co.	Consultant
Phyllis Tien, MD, MSc	Eli Lilly	Research Support
	Gilead Sciences	Research Support
	Merck & Co.	Research Support
Timothy M. Uyeki, MD, MPH	None	N/A
Alpana A. Waghmare, MD	AlloVir	Research Support
	Ansun Biopharma	Research Support
	Deverra Therapeutics	Data and Safety Monitoring Board Member
	KYORIN Pharmaceutical Co.	Advisory Board
	Pfizer	Research Support
	Vir Biotechnology	Research Support
Jinoos Yazdany, MD, MPH	AstraZeneca	Consultant and Research Support related to lupus
	Aurinia	Consultant, Consultation on lupus drug
	Bristol Myers Squibb	Research Support
	Pfizer	Consultant, Presentation

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