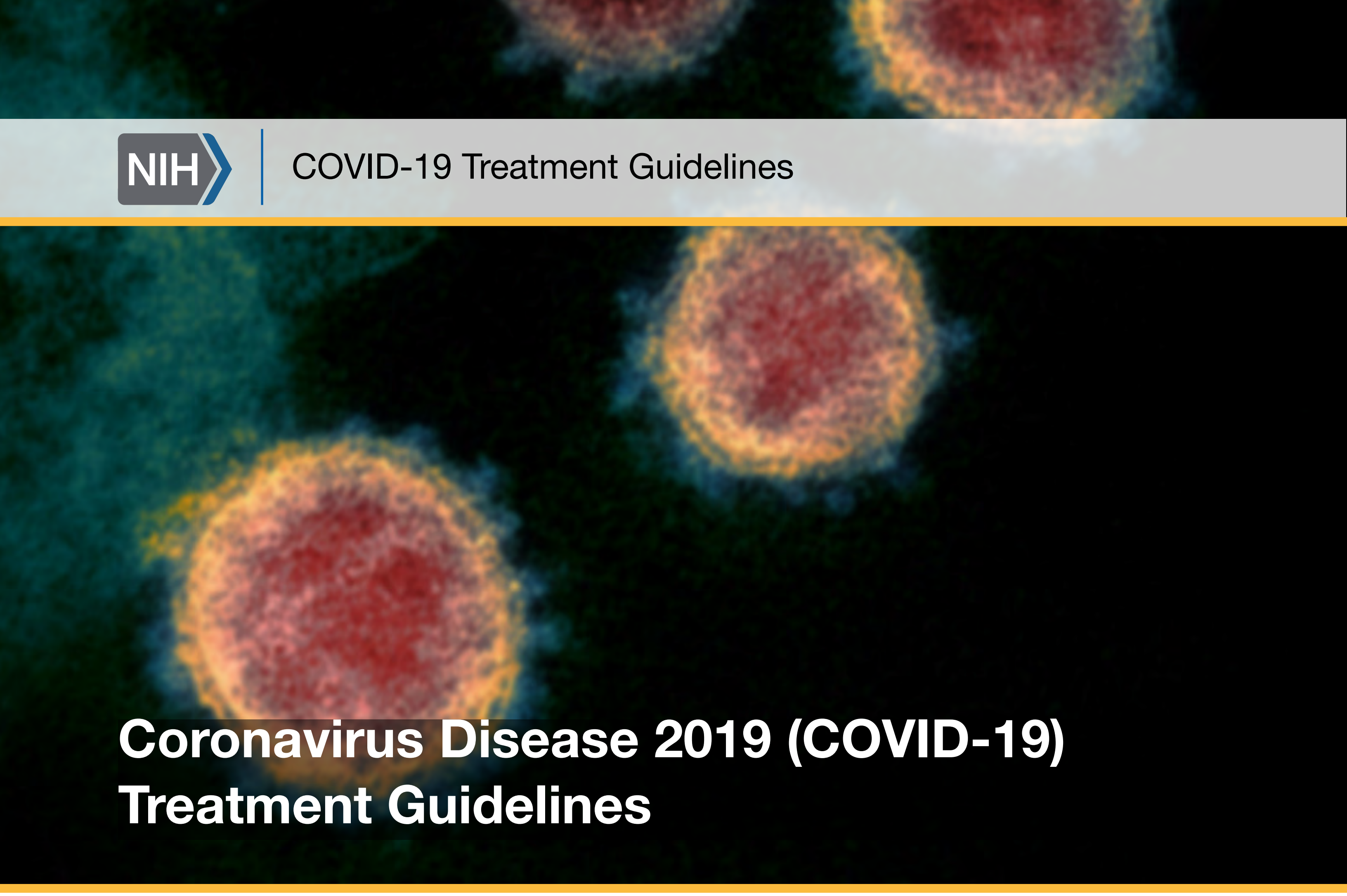

COVID-19 Treatment Guidelines

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: October 19, 2021

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

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

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

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

October 19, 2021

Key Updates to the Guidelines

Prevention of SARS-CoV-2 Infection

In this section, the Panel stresses that COVID-19 vaccination remains the most effective way to prevent SARS-CoV-2 infection. The key updates include:

Vaccine-Related Updates:

- The Centers for Disease Control and Prevention (CDC) recommends giving an additional dose of an mRNA COVID-19 vaccine to people who are at high risk of having suboptimal immune responses to a two-dose series. This dose should be given at least 28 days after the person receives the second dose of the two-dose series.
- Because the effectiveness of the BNT162b2 (Pfizer-BioNTech) vaccine may wane over time in some individuals, CDC recommends administering a booster dose of the vaccine to these individuals at least 6 months after they complete the primary series. People who received the primary series of the BNT162b2 vaccine but who have an increased risk of SARS-CoV-2 exposure or transmission may also receive a booster dose.
- The Panel has updated the information on vaccine-associated adverse effects, including myocarditis, pericarditis, and Guillain-Barré syndrome.

Anti-SARS-CoV-2 Monoclonal Antibodies for Post-Exposure Prophylaxis:

- A new subsection provides the Panel's recommendations for the use of either bamlanivimab plus etesevimab or casirivimab plus imdevimab as post-exposure prophylaxis (PEP) for those who have a history of exposure to individuals with SARS-CoV-2 infection and who are at high risk of progression to serious disease if they acquire the infection.
- The clinical trial data that support these recommendations are summarized in this section.

Clinical Spectrum of SARS-CoV-2 Infection

A new subsection entitled Infectious Complications in Patients With COVID-19 has been added to this section to discuss coinfections, reactivation of latent infection, nosocomial infections, and opportunistic fungal infections that may occur in patients with COVID-19.

Therapeutic Management of Nonhospitalized Adults With COVID-19

The text and figure have been updated to add bamlanivimab plus etesevimab as an anti-SARS-CoV-2 monoclonal antibody (mAb) combination option for the treatment of nonhospitalized patients with mild to moderate COVID-19 who are at high risk of progression to severe disease.

Oxygenation and Ventilation

The recommendations and rationale for performing awake prone positioning in nonmechanically ventilated adults have been updated. This section has also been reorganized and edited to improve readability.

Anti-SARS-CoV-2 Monoclonal Antibodies

In June 2021, the distribution of bamlanivimab plus etesevimab was paused in the United States because of the increase in the combined frequencies of two circulating SARS-CoV-2 variants: Gamma (P.1) and Beta (B.1.351). Since then, the Delta (B.1617.2, non-AY.1/AY.2) variant has become the predominant variant circulating in all states. Because the combination of bamlanivimab plus etesevimab retains activity against the Delta variant, the distribution of these anti-SARS-CoV-2 mAbs has resumed. The Panel now includes bamlanivimab plus etesevimab as a treatment option for nonhospitalized patients with mild to moderate COVID-19 who are at high risk for clinical progression. The information on the in vitro susceptibility of circulating variants to these mAbs and the potential activities of these mAbs against variants has been updated.

Interleukin-1 Inhibitors

The Panel has added recommendations to this section regarding canakinumab, a mAb that blocks interleukin-1 signaling. The Panel **recommends against** the use of **canakinumab** for the treatment of COVID-19, except in a clinical trial **(BIIa)**. This section also now includes a detailed discussion of the data on the use of anakinra from the SAVE-MORE, REMAP-CAP, and CORIMUNO-ANA-1 trials. There is no change to the Panel's recommendation for anakinra.

Interleukin-6 Inhibitors

This section has been updated to incorporate results from the sarilumab arm of the REMAP-CAP trial, an open-label, adaptive-platform randomized trial in patients with COVID-19 who were receiving invasive or noninvasive mechanical ventilation or cardiovascular support. This clinical trial data has been added to Table 4d as well.

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

This section now includes a detailed discussion of the COV-BARRIER trial of baricitinib and the STOP-COVID trial of tofacitinib. See Therapeutic Management of Hospitalized Adults With COVID-19 for the Panel's recommendations on the use of baricitinib and tofacitinib in hospitalized patients who require high-flow oxygen or noninvasive ventilation.

Other Updates to the Guidelines

The following sections have been updated to include new recommendations from CDC on administering an additional dose of the mRNA vaccines to certain people:

- Special Considerations in Adults and Children With Cancer
- Special Considerations in People With HIV
- Special Considerations in Solid Organ Transplant, Hematopoietic Stem Cell Transplant, and Cellular Immunotherapy Candidates, Donors, and Recipients

Minor changes have been made to the Overview of COVID-19 and Corticosteroids sections of the Guidelines.

October 7, 2021

Updated COVID-19 Treatment Guidelines Panel's Statement on the Prioritization of Anti-SARS-CoV-2 Monoclonal Antibodies for the Treatment or Prevention of SARS-CoV-2 Infection When There Are Logistical or Supply Constraints

The Panel has recommended using anti-SARS-CoV-2 mAbs for the treatment of mild to moderate COVID-19 and for PEP of SARS-CoV-2 infection in individuals who are at high risk for progression to severe COVID-19, as outlined in the Food and Drug Administration Emergency Use Authorizations issued for the anti-SARS-CoV-2 mAbs.

In a previous statement, the Panel suggested prioritization strategies to adopt when logistical constraints can make it difficult to administer anti-SARS-CoV-2 mAb therapy to all eligible patients.

The Panel has updated its previous statement on the prioritization of anti-SARS-CoV-2 mAbs to emphasize the following:

- To indicate that supply constraints, as well as logistical constraints, can make it impossible to administer anti-SARS-CoV-2 monoclonal mAbs to all eligible patients; *and*
- To recommend that, in addition to the prioritization strategies suggested in the previous statement, clinicians consider prioritizing the use of anti-SARS-CoV-2 mAb therapy for patients at highest risk of clinical progression. The updated statement includes a discussion of the risk factors for progression to severe COVID-19.

The Panel suggests prioritizing the use of anti-SARS-CoV-2 mAbs **only when triage becomes necessary due to logistical or supply constraints**.

Updated COVID-19 Treatment Guidelines Panel's Statement on the Prioritization of Anti-SARS-CoV-2 Monoclonal Antibodies for the Treatment or Prevention of SARS-CoV-2 Infection When There Are Logistical or Supply Constraints

Last Updated: October 7, 2021

The COVID-19 Treatment Guidelines Panel (the Panel) has recommended the use of anti-SARS-CoV-2 monoclonal antibodies (mAbs) for the treatment of mild to moderate COVID-19 and for post-exposure prophylaxis (PEP) of SARS-CoV-2 infection in individuals who are at high risk for progression to severe COVID-19, as outlined in the Food and Drug Administration Emergency Use Authorizations (EUAs) issued for the anti-SARS-CoV-2 mAbs. See Therapeutic Management of Nonhospitalized Adults With COVID-19 and the Panel's statements on the EUAs for bamlanivimab plus etesevimab and casirivimab plus imdevimab as PEP for SARS-CoV-2 infection for recommendation ratings and more detailed information.

The anti-SARS-CoV-2 mAbs are of greatest benefit as treatment or PEP for people who have risk factors for progression to severe COVID-19. Among individuals at high risk of progressing to severe COVID-19, the risks are lower for those who have been fully vaccinated and are immunocompetent than for those who are either not fully vaccinated or fully vaccinated but not expected to mount an adequate immune response to the vaccine.

The purpose of this statement is to provide guidance on which individuals might receive the greatest benefit from anti-SARS-CoV-2 mAb therapy when logistical or supply constraints make it impossible to offer the therapy to all eligible patients, and triage becomes necessary. **Only when it becomes necessary to triage the use of the anti-SARS-CoV-2 mAbs**, the Panel suggests:

- Prioritizing the treatment of COVID-19 over PEP of SARS-CoV-2 infection; *and*
- Prioritizing anti-SARS-CoV-2 mAb therapy for unvaccinated or incompletely vaccinated individuals and vaccinated individuals who are not expected to mount an adequate immune response (e.g., individuals who are immunocompromised or on immunosuppressive medications or individuals aged ≥65 years).

Providers should use their clinical judgment when prioritizing the use of anti-SARS-CoV-2 mAbs for treatment or PEP in a specific situation. The availability and distribution of authorized anti-SARS-CoV-2 mAbs should be monitored to ensure that access to the products is equitable.

Identifying Patients at Highest Risk of Progression to Severe COVID-19

When logistical or supply constraints limit the availability of anti-SARS-CoV-2 mAbs, the Panel recommends that, in addition to the prioritization strategies listed above, clinicians consider prioritizing their use for patients at highest risk of clinical progression. The Centers for Disease Control and Prevention (CDC) website provides a list of risk factors for severe illness from COVID-19. Some of the most important risk factors include (listed alphabetically) age (risk increases with each decade after age 50),[1] cancer, cardiovascular disease, chronic kidney disease, chronic lung disease, diabetes, immunocompromising conditions or receipt of immunosuppressive medications, obesity (body mass index ≥30), pregnancy, and sickle cell disease. 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 High Risk for Severe COVID-19. Of note, the likelihood of developing severe COVID-19 increases when a person has multiple comorbidities.[2]

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, as listed above. Children with obesity, moderate to severe immunosuppression, or those with complex chronic disease and medical complexity with respiratory technology dependence are at substantially increased risk of severe disease.[3]

The FDA EUAs provide a broad list of medical conditions or other factors as criteria for use of anti-SARS-CoV-2 mAbs as treatment or PEP. See the individual EUAs for the full list of these medical conditions and other factors.

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Introduction

Last Updated: July 8, 2021

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

Panel Composition

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

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

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

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

Development of the Guidelines

Each section of the Guidelines is developed by a working group of Panel members with expertise in the area addressed in the section. Each working group is responsible for identifying relevant information and published scientific literature and for conducting a systematic, comprehensive review of that information and literature. The working groups propose updates to the Guidelines based on the latest published research findings and evolving clinical information.

New Guidelines sections and recommendations are reviewed and voted on by the voting members of the Panel. To be included in the Guidelines, a recommendation statement must be endorsed by a majority of Panel members; this applies to recommendations for treatments, recommendations against treatments, and cases where there 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 considered during the development of the Guidelines confidential.

Method of Synthesizing Data and Formulating Recommendations

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

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

Table 1. Recommendation Rating Scheme

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

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

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

- **The Panel recommends using [blank] for the treatment of COVID-19 (rating).** Recommendations in this category are based on evidence from clinical trials or large cohort studies that demonstrate the clinical or virologic efficacy of a therapy in patients with COVID-19, with the potential benefits outweighing the potential risks.
- **There 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 the collective results from clinical trials and/or observational cohorts do not provide the evidence needed to support a recommendation due to too few or conflicting data.
- **The Panel recommends against the use of [blank] for the treatment of COVID-19, except in a clinical trial (rating).** This recommendation is used for an intervention that has not clearly demonstrated efficacy in the treatment of COVID-19 and/or has potential safety concerns. More clinical trials are needed to further define the role of the intervention.

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

Evolving Knowledge on Treatment for COVID-19

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

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

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

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

Overview of COVID-19

Last Updated: October 19, 2021

Epidemiology

The COVID-19 pandemic has exploded since cases were first reported in China in December 2019. As of October 18, 2021, more than 240 million cases of COVID-19—caused by SARS-CoV-2 infection—have been reported globally, including more than 4.9 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 those who were hospitalized was six times higher among those with reported medical conditions (45.4%) than among those without medical conditions (7.6%). The mortality rate was highest in those aged >70 years, regardless of the presence of chronic medical conditions. Among those with available data on health conditions, 32% had cardiovascular disease, 30% had diabetes, and 18% had chronic lung disease. Other conditions that may lead to a high risk for severe COVID-19 include cancer, kidney disease, 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 and subsequent hospitalization and death.[11-15] However, surveillance data that include race and ethnicity are not available for most reported cases of COVID-19 in the United States.[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 increases 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 may increase the risk of reinfection or decrease the efficacy of vaccines.[18] There is already 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]

Since December 2020, several variants have been identified that have now been assigned Greek letter designations by the World Health Organization (WHO). SARS-CoV-2 variants are designated as variants of concern (VOC) if they display certain characteristics, such as increased transmissibility or virulence. In addition, vaccines and/or therapeutics may have decreased effectiveness against VOC, and the mutations found in these variants may interfere with diagnostic test targets. The designation variant of interest (VOI) is used for important variants that have not yet been fully characterized; however, the designations and definitions for these variants differ between organizations.[20,21] In September 2021, the Centers for Disease Control and Prevention (CDC) added a new designation for variants: variants being monitored (VBM). This refers to variants for which the data indicate a potential or clear impact on approved or authorized medical countermeasures, or variants that have been 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. As such, these variants do not pose a significant and imminent risk to public health in the United States.

The B.1.617.2 (Delta) variant, which was first identified in India and has been designated a VOC, is the dominant variant in the United States since the summer of 2021. The Delta variant is more infectious than other variants, leading to increased transmissibility.[22] The B.1.1.7 (Alpha) variant that was first seen in the United Kingdom is more infectious and may be more virulent than earlier variants.[23-25] The B.1.351 (Beta) variant that was originally identified in South Africa has spread to many other countries, including the United States. The P.1 (Gamma) variant was originally identified in Manaus, Brazil, and has also emerged in the United States. These variants, which were previously designated as VOC, are now classified as VBM. Other VBM in the United States include the B.1.427/B.1.429 (Epsilon) variants that were originally identified in California, the B.1.526 (Iota) variant that was originally identified in New York, and the B.1.617.1 (Kappa) variant that was first identified in India. For a detailed discussion on the susceptibility of certain VOC, VOI , and VBM to available anti-SARS-CoV-2 mAbs, please see Anti-SARS-CoV-2 Monoclonal Antibodies.

The data on the emergence, spread, and clinical relevance of these new variants is 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, CoVariants.org, and WHO's Tracking SARS-CoV-2 Variants provide regular updates on the data for SARS-CoV-2 variants. The COVID-19 Treatment Guidelines Panel reviews the 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.[6,26,27] 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 [SpO_2] ≤93%, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen [PaO_2/FiO_2] <300 mm Hg, and/or lung infiltrates >50% within 24 to 48 hours), and 5% were critical (defined as respiratory failure, septic shock, and/or multiorgan dysfunction or failure).[28] 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 vary, but the most common are bilateral peripheral ground-glass opacities, with areas of consolidation developing later in the clinical course of COVID-19.[29] Imaging may be normal early in infection and can be abnormal in the absence of symptoms.[29]

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,[30,31] dermatologic,[32] hematologic,[33] hepatic,[34] neurologic,[35,36] renal,[37,38] and other complications. Thromboembolic events also occur in patients with COVID-19, with the highest risk occurring in critically ill patients.[39]

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).[40,41] Please see Special Considerations in Children for more information.

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Testing for SARS-CoV-2 Infection

Last Updated: April 21, 2021

Summary Recommendations
• To diagnose acute infection of SARS-CoV-2, the COVID-19 Treatment Guidelines Panel (the Panel) recommends using a nucleic acid amplification test (NAAT) with a sample collected from the upper respiratory tract (i.e., a nasopharyngeal, nasal, or oropharyngeal specimen) **(AIII)**. • For intubated and mechanically ventilated adults who are suspected to have COVID-19 but who do not have a confirmed diagnosis: • The Panel recommends obtaining lower respiratory tract samples to establish a diagnosis of COVID-19 if an initial upper respiratory tract sample is negative **(BII)**.   • The Panel recommends obtaining endotracheal aspirates over bronchial wash or bronchoalveolar lavage samples when collecting lower respiratory tract samples to establish a diagnosis of COVID-19 **(BII)**. • A NAAT should not be repeated in an asymptomatic person 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 who have received an initial diagnosis of infection; therefore, a NAAT should be considered for persons 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)**. • The Panel **recommends against** the use of serologic (i.e., antibody) testing to determine whether a person is immune to SARS-CoV-2 infection **(AIII)**.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional **Rating of Evidence:** I = One or more randomized trials 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, as well as 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. Ideally, diagnostic testing should also be performed for people who are likely to be at repeated risk of exposure to SARS-CoV-2, such as health care workers and first responders. Testing should also be considered for individuals who spend time in heavily populated environments (e.g., teachers, students, food industry workers) and for travelers. Testing requirements may vary by state, local, and employer policies. Travelers may need evidence of a recent negative test result to enter some states or countries; such documentation may be an acceptable alternative to quarantine upon arrival.

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

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

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

Nucleic Acid Amplification Testing for SARS-CoV-2 Infection

Reverse transcriptase polymerase chain reaction (RT-PCR)-based diagnostic tests (which detect viral nucleic acids) are considered the gold standard for detecting current SARS-CoV-2 infection. More recently, NAATs have included a variety of additional platforms (e.g., reverse transcriptase loop-mediated isothermal amplification [RT-LAMP]). Clinically, there may be a window period of up to 5 days after exposure before viral nucleic acids can be detected. 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.[3] 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 one 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.[4]

Many commercial NAATs that use RT-PCR rely on multiple targets to detect the virus, such that even if a mutation impacts one of the targets, the other RT-PCR targets will still work.[5] 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 variant that has been associated with increased transmission carries 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.[3]

SARS-CoV-2 poses several diagnostic challenges, including potentially discordant shedding of virus from the upper versus the lower respiratory tract. However, due to the high specificity of 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.[6-12] 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 careful consideration of the risk of exposing staff to infectious aerosols. Endotracheal aspiration appears to carry a lower risk of aerosol-generation than BAL, and some experts consider the sensitivity and specificity of endotracheal aspirates and BAL specimens comparable in detecting SARS-CoV-2.

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

NAATs can detect SARS-CoV-2 RNA in specimens obtained weeks to months after the onset of COVID-19 symptoms.[13,14] 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.[15,16] Furthermore, both virologic studies and contact tracing of high-risk contacts show a low risk for SARS-CoV-2 transmission after these intervals.[17,18] 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 **(AIII)**.[19] If there are concerns that an immunocompromised health care worker may still be infectious >20 days from the onset of SARS-CoV-2 infection, consultation with local employee health services regarding return-to-work testing policies is advised.

SARS-CoV-2 reinfection has been reported in people who have received an initial diagnosis of infection; therefore, a NAAT should be considered for persons 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, it should be noted that persons infected with SARS-CoV-2 may have a negative result on an initial NAAT and then have a positive result on a subsequent test due to intermittent detection of viral RNA and not due to reinfection.[13] 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 RT-PCR-based tests, but they have similarly high specificity. Antigen tests perform best early in the course of symptomatic SARS-CoV-2 infection, when the viral load is thought to be highest. Advantages of antigen-based tests are their low cost and rapid turnaround time. The availability of immediate results makes them an attractive option for point-of-care testing in high-risk congregate settings where preventing transmission is critical. Antigen-based tests also allow for repeat testing to quickly identify persons with SARS-CoV-2 infection.

Increasingly, data are available to guide the use of antigen tests as screening tests to detect or exclude SARS-CoV-2 infection in asymptomatic persons, or to determine whether a person who was previously confirmed to have SARS-CoV-2 infection is still infectious. The CDC has developed an antigen testing algorithm for persons 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.[20]

The CDC testing algorithm recommends additional NAATs 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 who is asymptomatic receives a positive result. Antigen tests can yield false positive results for a variety of reasons, including:

- Incomplete adherence to the instructions for antigen test performance (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)
- 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),[21-26] the Panel **does not recommend** serologic testing as the sole basis for diagnosing acute SARS-CoV-2 infection **(AIII)**. Because NAATs and antigen tests for SARS-CoV-2 occasionally yield false negative results, serologic tests have been used in some settings as an additional diagnostic test for patients who are strongly suspected to have SARS-CoV-2 infection. Using a serologic test in combination with a NAAT to detect IgG or total antibodies 3 to 4 weeks after symptom onset maximizes the sensitivity and specificity to detect past infection.

No serologic tests for SARS-CoV-2 are approved by the FDA; some, but not all, commercially available serologic tests for SARS-CoV-2 have received EUAs from the FDA.[1] Several professional societies and federal agencies, including the Infectious Diseases Society of America, the CDC, and the FDA, provide guidance on the use of serologic testing for SARS-CoV-2.

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

- Important performance characteristics 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). Serologic assays that have FDA EUAs should be used for public health and clinical use. Formal comparisons of serologic tests are in progress.
- Two types of serologic tests have received EUAs from the FDA. The first type are antibody tests that detect the presence of binding antibodies, which bind to a pathogen (e.g., a virus). The second type of tests detect neutralizing antibodies from recent or prior SARS-CoV-2 infection. It is unknown whether one type of test is more clinically meaningful than the other.
- Serologic assays may detect IgM, IgG, IgA, and/or total antibodies, or a combination of IgM and IgG antibodies. Serologic assays that detect IgG and total antibodies have higher specificity to detect past infection than assays that detect IgM and/or IgA antibodies or a combination of IgM and IgG antibodies.
- False positive test results may occur due to cross-reactivity from pre-existing antibodies to other coronaviruses.

Serologic Testing and Immunity to SARS-CoV-2 Infection

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

If SARS-CoV-2 antibodies are detected during a serologic test, the results should be interpreted with caution for the following reasons:

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

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

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

- Differentiate SARS-CoV-2 antibody responses to natural infection from vaccine-induced antibody responses to the SARS-CoV-2 spike protein antigen. Because nucleocapsid protein is not a constituent of vaccines that are currently available through EUAs or in late-stage clinical trials, serologic tests that detect antibodies by recognizing nucleocapsid protein can be used to distinguish antibody responses to natural infection from vaccine-induced antibody responses.
- Determine who may be eligible to donate convalescent plasma
- 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 (e.g., schools, dormitories, correctional facilities)
- Determine whether persons may return to the workplace
- Assess for prior infection solely to determine whether to vaccinate an individual
- Assess for immunity to SARS-CoV-2 following vaccination, except in clinical trials

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Prevention of SARS-CoV-2 Infection

Last Updated: October 19, 2021

Summary Recommendations
• The COVID-19 Treatment Guidelines Panel (the Panel) recommends COVID-19 vaccination for everyone who is eligible according to the Advisory Committee on Immunization Practices **(AI)**. • The Panel recommends using one of the following anti-SARS-CoV-2 monoclonal antibodies (listed alphabetically) as post-exposure prophylaxis (PEP) for people who are at high risk of progressing to severe COVID-19 if infected with SARS-CoV-2 **AND** who have the vaccination status **AND** exposure history outlined in the text below: • **Bamlanivimab 700 mg plus etesevimab 1,400 mg** administered as an intravenous (IV) infusion **(BIII)**; *or*   • **Casirivimab 600 mg plus imdevimab 600 mg** administered as subcutaneous injections **(AI)** or an IV infusion **(BIII)**. • The Panel **recommends against** the use of **hydroxychloroquine** for SARS-CoV-2 PEP **(AI)**. • The Panel **recommends against** the use of other drugs for SARS-CoV-2 PEP, except in a clinical trial **(AIII)**. • The Panel **recommends against** the use of any drugs for SARS-CoV-2 pre-exposure prophylaxis (PrEP), except in a clinical trial **(AIII)**.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional **Rating of Evidence:** I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

General Prevention Measures

Transmission of SARS-CoV-2 is thought to mainly occur through exposure to respiratory droplets transmitted to those within six feet of an infectious person. Less commonly, airborne transmission of small droplets and particles of SARS-CoV-2 to persons further than six 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 six 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 Centers for Disease Control and Prevention (CDC) recommendations for infection control and the appropriate use of personal protective equipment.[3]

Vaccination remains the most effective way to prevent SARS-CoV-2 infection. Anti-SARS-CoV-2 monoclonal antibodies (mAbs) may also be effective as post-exposure prophylaxis (PEP) for certain groups of people who are at risk of progression to serious COVID-19 and who have not been fully vaccinated or who are not expected to mount an adequate immune response to vaccines.

Vaccines

The COVID-19 Treatment Guidelines Panel (the Panel) recommends COVID-19 vaccination for everyone who is eligible for it according to the Advisory Committee on Immunization Practices **(AI)**. Currently, two mRNA vaccines are available in the United States. The two-dose series of the BNT162b2 (Pfizer-BioNTech) vaccine was approved by the Food and Drug Administration (FDA) for individuals aged ≥16 years, but it can be administered to individuals aged ≥12 years to <16 years under an Emergency Use Authorization (EUA). The two-dose series of the mRNA-1273 (Moderna) vaccine has an EUA for individuals aged ≥18 years. The FDA also issued an EUA for a single-dose human adenovirus type 26 (Ad26) vectored vaccine, Ad26.COV2.S (Johnson & Johnson/Janssen), for those aged ≥18 years. Clinical trials that are evaluating the use of these vaccines in younger age groups and clinical trials for other COVID-19 vaccine candidates are currently ongoing.[4]

In large placebo-controlled trials, the mRNA-1273 and BNT162b2 vaccines were >90% efficacious for preventing symptomatic, laboratory-confirmed COVID-19 and >95% efficacious for preventing severe COVID-19 after participants completed a two-dose series. The single-dose Ad26.COV2.S vaccine was 66% efficacious in preventing moderate to critical laboratory-confirmed COVID-19.[5-7] The available data on the COVID-19 vaccines that have received EUAs or FDA approval have demonstrated that these vaccines can markedly reduce the risk of infection, severe disease, hospitalization, and death. These vaccines have been shown to be effective against currently circulating SARS-CoV-2 variants,[8] although emerging data suggest some decrease in effectiveness against the Delta variant.[9] Surveillance to determine the long-term efficacy of these vaccines is ongoing.

Immunocompromised people who are vaccinated with an mRNA vaccine can have suboptimal antibody responses and may benefit from a third dose of the same vaccine.[10-12] Currently, CDC recommends that people who are moderately to severely immunocompromised receive an additional dose of the same mRNA vaccine product at least 28 days after the second dose of either the BNT162b2 or mRNA-1273 vaccine.[13] This includes people who have:

- Been receiving active cancer treatment for tumors or cancers of the blood
- Received an organ transplant and are taking immunosuppressive therapy
- Received a stem cell transplant within the last 2 years or who are taking immunosuppressive therapy
- Moderate or severe primary immunodeficiency (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome)
- Advanced or untreated HIV infection. Advanced HIV is defined as people with CD4 T lymphocyte cell counts <200/mm^3, a history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV.
- Active treatment with high-dose corticosteroids or other immunosuppressive drugs

There are currently insufficient data to determine whether recipients of the Ad26.COV2.S vaccine may benefit from an additional dose of the same vaccine.

COVID-19 Vaccine Booster

Data from recent studies suggest that the protection against SARS-CoV-2 infection provided by COVID-19 vaccination may decrease over time, and the vaccines may be less effective at protecting recipients against the Delta variant. Emerging evidence also shows that vaccine effectiveness against SARS-CoV-2 infection is decreasing over time among health care professionals and other frontline essential workers.[14,15] A small clinical trial reported that a BNT162b2 booster dose increased the vaccine-induced immune response in participants who had finished their primary series 6 months earlier.[16]

According to CDC recommendations, the following groups **should** receive a booster shot of the BNT162b2 COVID-19 vaccine at least 6 months after completing their primary series (i.e., the first two doses of the BNT162b2 vaccine):[17]

- People aged ≥65 years;
- Residents in long-term care settings who are aged ≥18 years; *and*

- People aged 50 to 64 years who have underlying medical conditions.[18]

CDC has also stated that the following groups **may** receive a booster shot of the BNT162b2 vaccine at least 6 months after completing their primary series, though clinicians should evaluate the benefits and risks of administering a booster shot to a given patient on a case-by-case basis:

- People aged 18 to 49 years who have underlying medical conditions;[18] *and*
- People aged 18 to 64 years who are at increased risk for SARS-CoV-2 exposure and transmission because of their occupational or institutional setting.[17]

Adverse Reactions

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). 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.[7,19]

Reports have suggested that there is an increased risk of thrombosis with thrombocytopenia in adults who have received the Ad26.COV2.S vaccine.[7] Most reports of this rare and serious condition have been in women aged 18 to 49 years.[20] Similar reports from Europe describe thrombocytopenia and venous thrombosis in patients who received the ChAdOx1 nCoV-19 (Oxford/AstraZeneca) vaccine, which uses a chimpanzee adenoviral vector.[21,22] 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 the type of thrombosis with thrombocytopenia that occurs in people who receive the Ad26.COV2.S vaccine. These considerations include information on administering a nonheparin anticoagulant and intravenous (IV) immunoglobulin to these patients.[23,24] Given the rarity of this syndrome and the unique treatment required, consider consulting a hematologist when treating these patients.

Myocarditis and pericarditis are rarely reported in people who have received COVID-19 vaccines, and most of the cases that have been reported were very mild and self-limiting. These conditions have occurred most often in male adolescents and young adults and people who have received mRNA vaccines.[25]

Guillain-Barré syndrome (GBS), a rare neurologic disorder, has been reported in approximately 12 people per million people who received the Ad26.COV2.S vaccine. 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.[25]

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 Fetal Medicine are recommending 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 now or who may become pregnant in the future.[4,26-31] The ACOG publication includes a guide to assist clinicians during conversations about COVID-19 vaccination with pregnant patients.[32]

Post-Exposure Prophylaxis

Anti-SARS-CoV-2 Monoclonal Antibodies

Vaccination remains the most effective way to prevent SARS-CoV-2 infection. However, despite widespread availability of COVID-19 vaccines, a number of individuals are either not fully vaccinated or cannot mount adequate responses to the vaccine. Some of these individuals, if infected, are at high risk of progressing to serious COVID-19. Based on the results of two large randomized controlled trials, the FDA expanded the EUA indication for the anti-SARS-CoV-2 mAbs bamlanivimab plus etesevimab and casirivimab plus imdevimab to allow these combinations to be used as PEP for selected individuals.[33]

Recommendations

The Panel recommends using one of the following anti-SARS-CoV-2 mAbs (listed alphabetically) as PEP for people who are at high risk for progressing to severe COVID-19 if infected with SARS-CoV-2 **AND** who have the vaccination status **AND** exposure history outlined in the text below.

- **Bamlanivimab 700 mg plus etesevimab 1,400 mg** administered as an IV infusion **(BIII)**; *or*
- **Casirivimab 600 mg plus imdevimab 600 mg** administered as subcutaneous (SQ) injections **(AI)** or an IV infusion **(BIII)**.

Vaccination Status:

- Not fully vaccinated (defined as people who were never vaccinated, those who received the first dose of a two-dose series, or those who received the second dose of a two-dose series or a single-dose vaccine <2 weeks ago); *or*
- Fully vaccinated, but not expected to mount an adequate immune response (e.g., those with immunocompromising conditions, including those who are taking immunosuppressive medications).

AND

Exposure History to SARS-CoV-2:

- Had a recent exposure to an individual with SARS-CoV-2 infection that is consistent with CDC close contact criteria; *or*
- At high risk of exposure to an individual with SARS-CoV-2 infection because of a recent occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (e.g., nursing homes, prisons).

The doses should be administered as soon as possible and preferably within 7 days of high-risk exposure **(BIII)**. The patient should be observed for at least 1 hour after the injections or infusion.

It should be noted that even though the EUA calls for the combination of bamlanivimab 700 mg plus etesevimab 1,400 mg administered as a single IV infusion, the clinical trial that was used to support the EUA only studied bamlanivimab monotherapy at a single dose of 4,200 mg (see Anti-SARS-CoV-2 Monoclonal Antibodies).

The EUA for casirivimab plus imdevimab allows for repeat dosing of casirivimab 300 mg plus imdevimab 300 mg once every 4 weeks using SQ injections or an IV infusion for those who meet the EUA criteria for PEP and have ongoing exposures. However, there are no data from the COVID-19 Phase 3 Prevention Trial or other studies on the utility of repeat dosing for individuals who continue to have high-risk exposures. Therefore, the Panel finds that there is insufficient evidence to recommend either for or against repeat dosing every 4 weeks for those who received PEP and who continue to have high-risk exposures.

If there are shortages of anti-SARS-CoV-2 mAbs or logistical constraints (e.g., limited space, not enough staff who can administer therapy), it may be difficult to administer these agents to all eligible patients. In situations where it is necessary to triage eligible patients, the Panel suggests prioritizing the treatment of COVID-19 over PEP. For further guidance on prioritizing the use of these mAbs, see this statement from the Panel.

Clinical Trial Data for Bamlanivimab Monotherapy

BLAZE-2 is a randomized, double-blind, Phase 3 trial that enrolled residents and staff of 74 skilled nursing and assisted living facilities in the United States. Each facility had had at least one confirmed index case of SARS-CoV-2 infection, and the staff and residents had no known history of COVID-19.[34] All participants provided both nasal and nasopharyngeal (NP) swabs for reverse transcription polymerase chain reaction (RT-PCR)-based diagnostic tests and blood for SARS-CoV-2 antibody testing. Nasal and NP swabs were obtained weekly for 57 days.

Participants who were found to be RT-PCR and antibody negative were considered the prevention population. Between August and November 2020, the study randomized 1,175 participants 1:1 to receive either bamlanivimab monotherapy at a dose of 4,200 mg or placebo by IV infusion. The prevention population included 484 participants who received bamlanivimab (323 staff and 161 residents) and 482 participants who received placebo (343 staff and 139 residents). The baseline characteristics of the staff and resident populations were very different; for example, the residents had a median age that was >30 years higher than the staff (76 years vs. 43 years) and had greater risks for disease progression.

In the overall prevention population, 114 participants (11.9%) experienced mild or worse COVID-19 by Day 57. There was a significantly lower incidence of mild or worse COVID-19 in the bamlanivimab arm than in the placebo arm (8.5% vs. 15.2%; OR 0.43; 95% CI, 0.28–0.68; $P < 0.001$), with an absolute risk difference of -6.6 percentage points (95% CI, -10.7 to -2.6). The difference was most significant in the resident population, where the incidence of mild or worse COVID-19 was 8.8% in the in bamlanivimab arm compared to 22.5% in the placebo arm (OR 0.20; 95% CI, 0.08–0.49; $P < 0.001$), with an absolute difference of -13.7 percentage points (95% CI, -21.9 to -5.4). In contrast, the difference between the bamlanivimab and placebo arms did not achieve statistical significance in the staff prevention population. Similar findings were observed for the secondary endpoint of the incidence of moderate or worse COVID-19.

In the prevention population, 198 participants (20.6%) had positive RT-PCR results within 4 weeks of randomization. The frequency of positive results was significantly lower in the bamlanivimab arm than in the placebo arm (17.9% vs. 23.3%; OR 0.66; 95% CI, 0.46–0.94; P = 0.02), with an absolute risk difference of -5.4 percentage points (95% CI, -10.5 to -0.3). The difference was significant for the resident prevention population but not the staff prevention population. An additional secondary endpoint in this study was mortality due to COVID-19; a total of four participants died, all of whom were residents who were randomized to receive placebo.

The overall safety population included 1,175 participants. Serious adverse events were reported in 3.7% of bamlanivimab recipients and 3.2% of placebo recipients. Any adverse events were reported in 20.1% of participants in the bamlanivimab arm and 18.9% of those in the placebo arm. The types of events were balanced across the study arms. Hypersensitivity reactions that occurred within 24 hours of study product infusion were reported in three participants (0.5%) in the bamlanivimab arm and none in the placebo arm.

Clinical Trial Data for Casirivimab Plus Imdevimab

Casirivimab plus imdevimab was evaluated as PEP in a randomized, double-blind, placebo-controlled Phase 3 trial that was conducted at 112 sites in the United States, Romania, and Moldova.[35] The trial enrolled individuals aged ≥12 years who were exposed to a household contact (the index patient) who had a positive SARS-CoV-2 RT-PCR result from a NP swab specimen that was collected within the previous 96 hours. Study participants were asymptomatic, had a negative NP RT-PCR result for SARS-CoV-2, and intended to live with the index patient for the 28-day duration of follow-up.

Participants were randomized 1:1 to receive casirivimab 600 mg plus imdevimab 600 mg or placebo administered as four SQ injections (2.5 mL per injection) at different sites. NP swabs were collected weekly. The primary efficacy endpoint was the proportion of participants who developed symptomatic, RT-PCR-confirmed SARS-CoV-2 infection during the 28 days of follow-up. Additional key efficacy endpoints included asymptomatic infection and the quantity and duration of viral shedding detected by NP swabs.

The primary analysis included 1,505 participants (753 in the casirivimab plus imdevimab arm and 752 in the placebo arm) who had negative SARS-CoV-2 RT-PCR results at baseline and who were subsequently found to be serum SARS-CoV-2 antibody negative. The mean age was 42.9 years, 45.9% of participants were men, and 9.3% of participants were Black or African American and 40.5% were Hispanic/Latino. The protocol-specified risk factors for progression to severe COVID-19 were present in 30.5% of participants, with approximately 75% meeting the high-risk criteria in the revised EUA.

The use of casirivimab plus imdevimab resulted in a significant reduction in the risk of symptomatic SARS-CoV-2 infection when compared with placebo (81.4% risk reduction: 11 of 753 participants [1.5%] vs. 59 of 752 patients [7.8%]; OR 0.17; $P < 0.001$). This risk reduction was present throughout the follow-up period, starting from the first week and continuing through Week 4. Using both asymptomatic and symptomatic infections as an endpoint, the use of casirivimab plus imdevimab was associated with a significant reduction in risk compared to placebo (66.4% risk reduction; 36 of 753 participants [4.8%] vs. 107 of 752 participants [14.2%]; OR 0.31; 95% CI, 0.21–0.46; $P < 0.0001$). Among the subset of participants who were found to be seropositive at baseline (and were therefore excluded from the primary analysis), only a small number of participants reached the study endpoints, and there was no significant difference in the number who reached the endpoints between the casirivimab plus imdevimab arm (1 of 235 patients [0.4%]) and the placebo arm (5 of 222 participants [2.3%]; OR 0.19; 95% CI, 0.02–1.68; $P = 0.14$).

Hospitalizations were rare, with no hospitalized participants in the casirivimab plus imdevimab arm and four in the placebo arm. Some participants in the study received casirivimab plus imdevimab before they received their RT-PCR results; among these participants, those who eventually received positive RT-PCR results had a shorter duration of viral detection than the participants in the placebo arm (mean of 1.1 vs. 2.2 weeks). The frequencies of adverse events were similar between the two arms.

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.[36,37] A small cohort study without a control group suggested that hydroxychloroquine might reduce the risk of SARS-CoV-2 transmission to close contacts.[38] There have been several large trials to determine whether hydroxychloroquine can reduce the risk of infection after exposure to infected individuals. These studies used different dosing 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.[39-41]

Other Drugs for PEP

- 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.[42,43] Population data indicated that country-wide, mass-use of prophylactic chemotherapy for parasitic infections, including the use of ivermectin, was associated with a lower incidence of COVID-19.[44] At this time, few clinical trials have evaluated the safety and efficacy of using ivermectin for SARS-CoV-2 pre-exposure prophylaxis (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 COVID-19, no cases of SARS-CoV-2 infection were identified within 21 days of initiating ivermectin for PEP.[45] 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.[46]

Pre-Exposure Prophylaxis

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

Rationale

At present, there is no known agent that is effective in preventing infection when administered before exposure to SARS-CoV-2 (i.e., as PrEP). Clinical trials are investigating several agents, including emtricitabine plus tenofovir alafenamide or tenofovir disoproxil fumarate, hydroxychloroquine, ivermectin, and supplements such as zinc, vitamin C, and vitamin D. Studies of anti-SARS-CoV-2 mAbs that target SARS-CoV-2 are also underway. 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 for being exposed to infected individuals, such as healthcare 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.[47] 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.[48] Neither study demonstrated any evidence of a reduction in rate of acquiring infection. Both studies reported an increased frequency of mild adverse events in the treatment group.

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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.

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.

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 Adult Patients 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.

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 General Considerations for information on PICS).[37,38]

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 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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Clinical Management Summary

Last Updated: October 19, 2021

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 1. Therapeutic Management of NonHospitalized Adults With COVID-19

All outpatients with COVID-19 who enter the health care system should have in-person or telehealth follow-up visits. Symptomatic treatments, including hydration, antipyretics, analgesics, and antitussives, can be initiated as needed.

Patients should be counseled about symptoms that warrant re-evaluation by a health care provider (e.g., new onset dyspnea, worsening dyspnea [particularly dyspnea that occurs while the patient is resting or that interferes with daily activities], mental status changes). Home resources should be assessed before patients are discharged from a clinic, urgent care center, ED, or hospital; outpatients should have access to housing, proper nutrition, a caregiver, and a device that is suitable for telehealth. If patients are discharged while they are still receiving oxygen supplementation, they should receive oximetry monitoring and close follow-up soon after discharge.

PATIENT DISPOSITION	PANEL'S RECOMMENDATIONS
Not Requiring Hospitalization or Supplemental Oxygen, As Determined by a Health Care Provider During an ED, In-Person, or Telehealth Visit	Anti-SARS-CoV-2 mAb products are recommended for outpatients with mild to moderate COVID-19 who are at high risk of disease progression, as defined by the EUA criteria (treatments are listed in alphabetical order, and they may change based on circulating variants):[a] • **Bamlanivimab plus etesevimab**; *or* • **Casirivimab plus imdevimab**; *or* • **Sotrovimab** The Panel **recommends against** the use of **dexamethasone** or **other systemic glucocorticoids** in the absence of another indication **(AIII)**.[b]
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 (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*[c]	There is insufficient evidence to recommend either for or against the continued use of remdesivir, dexamethasone, and/or baricitinib. Review the text below when considering the use of any of these agents after hospital discharge.
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*[d]	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)**. There is insufficient evidence to recommend either for or against the use of remdesivir. When considering the use of remdesivir, review the text below for more information. The Panel **recommends against** the use of **baricitinib** in this setting, except in a clinical trial **(AIII)**.

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

[a] In laboratory studies, some CDC SARS-CoV-2 VOC, VBM, or VOI that harbor certain mutations have reduced susceptibility to certain agents. However, the impact of these mutations on a patient's clinical response varies, as do the proportions of these variants in different geographic regions. See Anti-SARS-CoV-2 Monoclonal Antibodies for more information. Updates on the distribution of bamlanivimab and etesevimab are available on the HHS Bamlanivimab/Etesevimab website.

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

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

[d] In cases where 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 (whether patients are receiving oxygen at home for the first time or are increasing their baseline oxygen requirements), pulse oximetry, and close follow-up through visiting nurse services, telehealth, or in-person clinic visits.

Key: AE = adverse events; CDC = Centers for Disease Control and Prevention; ED = emergency department; EUA = Emergency Use Authorization; HHS = Department of Health and Human Services; mAb = monoclonal antibody; the Panel = the COVID-19 Treatment Guidelines Panel; PO = orally; VBM = variants being monitored; VOC = variants of concern; VOI = variants of interest

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

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS
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 at high risk of disease progression, remdesivir may be appropriate.
Hospitalized and Requires Supplemental Oxygen	Use one of the following options: • **Remdesivir**[b] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone plus remdesivir**[b] (e.g., for patients who require increasing amounts of supplemental oxygen) **(BIII)** • **Dexamethasone** (when combination with remdesivir cannot be used or is not available) **(BI)**
Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	Use one of the following options: • **Dexamethasone (AI)** • **Dexamethasone plus remdesivir**[b] **(BIII)** For recently hospitalized[c] patients with rapidly increasing oxygen needs and systemic inflammation: • Add either **baricitinib (BIIa)** or **IV tocilizumab (BIIa)** to one of the two options above[d] • If neither baricitinib nor IV tocilizumab is available or feasible to use, **tofacitinib** can be used instead of baricitinib **(BIIa)** or **IV sarilumab** can be used instead of IV tocilizumab **(BIIa)**.
Hospitalized and Requires IMV or ECMO	• **Dexamethasone (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)**.

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

[a] Corticosteroids prescribed for an underlying condition should be continued.
[b] If patients progress to requiring high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO, complete remdesivir course.
[c] For example, within 3 days of hospital admission.
[d] Drugs are listed alphabetically and not in order of preference. As there are no studies directly comparing baricitinib and tocilizumab for treatment of COVID-19, there is insufficient evidence to recommend one drug over the other. Treatment decisions should be determined by local guidance, drug availability, and patient comorbidities.

Key: ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; IMV = invasive mechanical ventilation; IV = intravenous; the Panel = the COVID-19 Treatment Guidelines Panel; PO = orally

General Management of Nonhospitalized Patients With Acute COVID-19

Last Updated: July 8, 2021

Summary Recommendations
• Management of nonhospitalized patients with acute COVID-19 should include providing supportive care, 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 before receiving in-person care. 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 = Optional **Rating of Evidence:** I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

Introduction

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 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). Management of COVID-19 patients in the outpatient setting should focus on providing supportive care, taking steps to reduce the risk of SARS-CoV-2 transmission (e.g., wearing a mask, isolating the patient),[4,5] and advising 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 suspected or laboratory-confirmed COVID-19 should be triaged via telehealth visits before they receive an in-person evaluation. 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. 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 associated with 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.

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 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 for 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 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 one 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 (see the Panel's statement on the EUAs for anti-SARS-CoV-2 monoclonal antibodies).

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: October 19, 2021

Figure 1 outlines the COVID-19 Treatment Guidelines Panel's (the Panel) recommendations for using therapeutic interventions outside the hospital inpatient setting. These recommendations differ depending on the patient's disposition.

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

All outpatients with COVID-19 who enter the health care system should have in-person or telehealth follow-up visits. Symptomatic treatments, including hydration, antipyretics, analgesics, and antitussives, can be initiated as needed.

Patients should be counseled about symptoms that warrant re-evaluation by a health care provider (e.g., new onset dyspnea, worsening dyspnea [particularly dyspnea that occurs while the patient is resting or that interferes with daily activities], mental status changes). Home resources should be assessed before patients are discharged from a clinic, urgent care center, ED, or hospital; outpatients should have access to housing, proper nutrition, a caregiver, and a device that is suitable for telehealth. If patients are discharged while they are still receiving oxygen supplementation, they should receive oximetry monitoring and close follow-up soon after discharge.

PATIENT DISPOSITION	PANEL'S RECOMMENDATIONS
Not Requiring Hospitalization or Supplemental Oxygen, As Determined by a Health Care Provider During an ED, In-Person, or Telehealth Visit	Anti-SARS-CoV-2 mAb products are recommended for outpatients with mild to moderate COVID-19 who are at high risk of disease progression, as defined by the EUA criteria (treatments are listed in alphabetical order, and they may change based on circulating variants):[a] • **Bamlanivimab plus etesevimab**; *or* • **Casirivimab plus imdevimab**; *or* • **Sotrovimab** The Panel **recommends against** the use of **dexamethasone** or **other systemic glucocorticoids** in the absence of another indication **(AIII)**.[b]
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 (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*[c]	There is insufficient evidence to recommend either for or against the continued use of remdesivir, dexamethasone, and/or baricitinib. Review the text below when considering the use of any of these agents after hospital discharge.
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*[d]	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)**. There is insufficient evidence to recommend either for or against the use of remdesivir. When considering the use of remdesivir, review the text below for more information. The Panel **recommends against** the use of **baricitinib** in this setting, except in a clinical trial **(AIII)**.

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

[a] In laboratory studies, some CDC SARS-CoV-2 VOC, VBM, or VOI that harbor certain mutations have reduced susceptibility to certain agents. However, the impact of these mutations on a patient's clinical response varies, as do the proportions of these variants in different geographic regions. See Anti-SARS-CoV-2 Monoclonal Antibodies for more information. Updates on the distribution of bamlanivimab and etesevimab are available on the HHS Bamlanivimab/Etesevimab website.

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

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

[d] In cases where 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 (whether patients are receiving oxygen at home for the first time or are increasing their baseline oxygen requirements), pulse oximetry, and close follow-up through visiting nurse services, telehealth, or in-person clinic visits.

Key: AE = adverse events; CDC = Centers for Disease Control and Prevention; ED = emergency department; EUA = Emergency Use Authorization; HHS = Department of Health and Human Services; mAb = monoclonal antibody; the Panel = the COVID-19 Treatment Guidelines Panel; PO = orally; VBM = variants being monitored; VOC = variants of concern; VOI = variants of interest

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

Anti-SARS-CoV-2 Monoclonal Antibodies

Two combination anti-SARS-CoV-2 monoclonal antibody (mAb) products (bamlanivimab plus etesevimab and casirivimab plus imdevimab) and a single mAb (sotrovimab) have been shown to reduce the risk of hospitalization and death in the outpatient setting in those with mild to moderate COVID-19 symptoms and certain risk factors for disease progression. As a result, these products have received Emergency Use Authorizations (EUAs) from the Food and Drug Administration (FDA) for the treatment of COVID-19 in these individuals, as well as in those with other risk factors for progression that have been identified in population-based studies. There are no comparative data to determine whether there are differences in clinical efficacy or safety between these products.

The Panel recommends using one of the following anti-SARS-CoV-2 mAbs to treat outpatients with mild to moderate COVID-19 who are at high risk of clinical progression, as defined by the EUA criteria (treatments are listed in alphabetical order, and they may change based on circulating variants):

- **Bamlanivimab plus etesevimab**; *or*
- **Casirivimab plus imdevimab**; *or*
- **Sotrovimab**

The availability of bamlanivimab and etesevimab is restricted in areas with an elevated prevalence of variants that have markedly reduced in vitro susceptibility to these agents (e.g., the Gamma and Beta variants). Please see this statement from the Department of Health and Human Services for an update on the distribution of bamlanivimab and etesevimab.

The Delta (B.1.617.2, non-AY.1/AY.2) variant is currently the predominant variant of concern (VOC) in the United States. This VOC retains in vitro susceptibility to all the anti-SARS-CoV-2 mAbs that are currently available through EUAs.[3,4]

Treatment should be started as soon as possible after the patient receives a positive result on a SARS-CoV-2 antigen test or a nucleic acid amplification test (NAAT) and within 10 days of symptom onset. When logistical or supply constraints limit the availability of anti-SARS-CoV-2 mAbs, the Panel recommends prioritizing the treatment of patients who are at the highest risk of clinical progression (see the Panel's statement on prioritizing the use of anti-SARS-CoV-2 mAbs). For more details on the available clinical trial data for these antibodies, see Anti-SARS-CoV-2 Monoclonal Antibodies and Table 3a.

The Centers for Disease Control and Prevention recommends deferring COVID-19 vaccination for at least 90 days in those who have received anti-SARS-CoV-2 mAbs. This is a precautionary measure, as the antibody treatment may interfere with vaccine-induced immune responses. In people who are vaccinated and then develop COVID-19, prior receipt of a vaccine should not affect treatment decisions, including the use of and timing of treatment with mAbs.[5]

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. There was no observed benefit of dexamethasone in hospitalized patients who did not receive oxygen support.[6] Nonhospitalized patients who did not require supplemental oxygen were not included in this trial; therefore, the safety and efficacy of corticosteroids in this population have not been established. 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)**. Moreover, 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.

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. The practice of discharging inpatients who still require oxygen 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. Data that support the use of corticosteroids after discharge are limited. The main concern is that discharged patients cannot be closely monitored for the toxicities that are associated with corticosteroid use, which include increased blood glucose levels and neuropsychiatric impairment. 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 be carefully monitored for adverse events. These individuals should receive oximetry monitoring and close follow-up through telehealth, visiting nurse services, or in-person clinic visits.

In rare cases, patients with COVID-19 who require supplemental oxygen and hospital admission may need to be discharged from the emergency department (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 orally 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 clinic visits.

Remdesivir

Remdesivir is currently the only drug that is approved by the FDA for the treatment of COVID-19. It is recommended for use in hospitalized patients who require supplemental oxygen. The clinical trials that evaluated the safety and efficacy of remdesivir stopped this treatment at the time of discharge from the hospital.[7-9] The Panel **recommends against** the continuation of **remdesivir** in hospitalized patients with COVID-19 who are stable enough for discharge and who do not require supplemental oxygen **(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. There is insufficient evidence to recommend either for or against the continued use of remdesivir after hospital discharge in patients who require supplemental oxygen. Since remdesivir can only be administered by intravenous infusion, there may be logistical issues with providing remdesivir to outpatients. If remdesivir is provided, it should only be administered in health care settings that can provide a similar level of care to an inpatient hospital. These individuals should receive oximetry monitoring and close follow-up through telehealth, visiting nurse services, or in-person clinic 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). There is insufficient evidence to recommend either for or against the routine use of remdesivir in this setting. If remdesivir is provided, it should only be administered in health care settings that can provide a similar level of care to an inpatient hospital. These individuals should receive oximetry monitoring and close follow-up through telehealth, visiting nurse services, or in-person clinic visits.

Baricitinib

The pivotal safety and efficacy trials for baricitinib enrolled hospitalized patients with COVID-19, and treatment was stopped at the time of hospital discharge.[10,11] The Panel **recommends against** the continuation of **baricitinib** in hospitalized patients with COVID-19 who are stable enough for discharge and who do not require supplemental oxygen **(AIIa)**.

There is insufficient evidence to recommend either for or against the continued use of baricitinib after hospital discharge in patients who have been discharged from the inpatient setting but who still require supplemental oxygen.

There are currently no data that assess the safety and efficacy of using baricitinib in patients who require supplemental oxygen and hospital admission, but who have been discharged from the ED due to scarce resources. Therefore, the Panel **recommends against** the use of **baricitinib** in these patients, except in a clinical trial **(AIII)**.

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 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** and **fluvoxamine**
  - Supplements, such as **vitamin C**, **vitamin D**, and **zinc**
- **Anticoagulants and antiplatelet therapy** should not be initiated in the outpatient setting 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 **(AIII)**. 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 Certain 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.[12] 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.

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Therapeutic Management of Hospitalized Adults With COVID-19

Last Updated: August 25, 2021

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

Dosing regimens and duration of therapy for the drugs recommended in this figure are listed in Table A below.

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS
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 at high risk of disease progression, remdesivir may be appropriate.
Hospitalized and Requires Supplemental Oxygen	Use one of the following options: • **Remdesivir**[b] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone plus remdesivir**[b] (e.g., for patients who require increasing amounts of supplemental oxygen) **(BIII)** • **Dexamethasone** (when combination with remdesivir cannot be used or is not available) **(BI)**
Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	Use one of the following options: • **Dexamethasone (AI)** • **Dexamethasone plus remdesivir**[b] **(BIII)** For recently hospitalized[c] patients with rapidly increasing oxygen needs and systemic inflammation: • Add either **baricitinib (BIIa)** or **IV tocilizumab (BIIa)** to one of the two options above[d] • If neither baricitinib nor IV tocilizumab is available or feasible to use, **tofacitinib** can be used instead of baricitinib **(BIIa)** or **IV sarilumab** can be used instead of IV tocilizumab **(BIIa)**.
Hospitalized and Requires IMV or ECMO	• **Dexamethasone (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)**.

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

[a] Corticosteroids prescribed for an underlying condition should be continued.
[b] If patients progress to requiring high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO, complete remdesivir course.
[c] For example, within 3 days of hospital admission.
[d] Drugs are listed alphabetically and not in order of preference. As there are no studies directly comparing baricitinib and tocilizumab for treatment of COVID-19, there is insufficient evidence to recommend one drug over the other. Treatment decisions should be determined by local guidance, drug availability, and patient comorbidities.

Key: ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; IMV = invasive mechanical ventilation; IV = intravenous; the Panel = the COVID-19 Treatment Guidelines Panel; PO = orally

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

Drug Name	Dosing Regimen	Comments
Remdesivir	Remdesivir 200 mg IV once, then remdesivir 100 mg IV once daily for 4 days or until hospital discharge	• Treatment may be extended for up to 10 days if there is no substantial clinical improvement by Day 5. • If the patient progresses to more severe illness, complete the course of remdesivir. • eGFR <30 mL/min/1.73 m^2: Remdesivir **is not recommended**.
Dexamethasone	Dexamethasone 6 mg IV or PO once daily for up to 10 days or until hospital discharge	• If dexamethasone is not available, an equivalent dose of another corticosteroid may be used. • See the Corticosteroids section for more information.
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**.
Tofacitinib	Tofacitinib 10 mg PO twice daily for up to 14 days or until hospital discharge	• Use as an alternative 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
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, pre-filled syringe (not the pre-filled pen) for SQ injection. Reconstitute sarilumab 400 mg in 100 cc 0.9% NaCl and administer as an IV infusion over 1 hour.	• Use as an alternative if tocilizumab is not available or not feasible to use **(BIIa)**. • In the United States, the currently approved route of administration for sarilumab is SQ injection. In the REMAP-CAP trial, the SQ formulation was used to prepare the IV infusion.

Key: eGFR = estimated glomerular filtration rate; IV = intravenous; PO = oral; SQ = subcutaneous

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 in these patients for the treatment of COVID-19, but use may be appropriate in patients 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] In participants who did not require supplemental oxygen at enrollment, no survival benefit was observed for dexamethasone: 17.8% of participants in the dexamethasone arm and 14% in the control arm died within 28 days of enrollment (rate ratio 1.19; 95% CI, 0.91–1.55). 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 this subgroup, unless the patient has another indication for corticosteroid therapy.

Rationale for the Panel's Assessment That There Is Insufficient Evidence to Recommend Either for or Against the Use of Remdesivir

The ACTT-1 trial was a multinational randomized controlled trial that compared remdesivir to placebo in hospitalized patients with COVID-19. Remdesivir showed no significant benefit in patients with mild to moderate disease, which was defined as oxygen saturation >94% on room air or a respiratory rate <24 breaths/min without supplemental oxygen (rate ratio for recovery 1.29; 95% CI, 0.91–1.83); however, there were only 138 patients in this group.[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 seven-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 (control arm). About 25% of hospitalized patients in both arms did not require supplemental oxygen at study entry. The primary outcome of in-hospital mortality occurred in 11 of 661 patients (2%) in the remdesivir arm and in 13 of 664 patients (2.1%) in the control arm (rate ratio 0.90; 99% CI, 0.31–2.58).[4] The open-label design of this study makes it difficult to determine whether remdesivir affects recovery time as determined by duration of hospitalization because patient discharge may have been delayed in order to complete remdesivir therapy. Please see Table 2a for additional information.

Because these trials produced conflicting results regarding 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 judge that remdesivir is appropriate for some hospitalized patients with moderate disease (e.g., in cases where a person is at a particularly high risk for clinical deterioration).

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

Recommendations

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

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

Additional Considerations

- If dexamethasone is not available, an alternative corticosteroid such as **prednisone**, **methylprednisolone**, or **hydrocortisone** can be used **(BIII)**. See Corticosteroids for dosing recommendations.
- There is insufficient evidence to determine which patients in this group would benefit from adding baricitinib or tocilizumab to dexamethasone treatment. Some Panel members would add

baricitinib or tocilizumab to a patient's dexamethasone treatment in cases where the patient has rapidly increasing oxygen needs and increased markers of inflammation but does not yet require high-flow oxygen or noninvasive ventilation.

- As there are no studies that directly compare using baricitinib and tocilizumab as treatments for COVID-19, the Panel has insufficient evidence to recommend one drug over the other. Treatment decisions should be made based on local guidance, drug availability, and patient comorbidities.

Rationale for the Use of Remdesivir

In the ACTT-1 trial, remdesivir was associated with improved time to recovery in the 435 participants who required oxygen supplementation but not high-flow oxygen, noninvasive ventilation, or invasive 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, invasive 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 patients who progressed to invasive 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.

Based on the results of the ACTT-1 trial, the Panel recommends **remdesivir** (without dexamethasone) as a treatment option for certain patients who require supplemental oxygen (e.g., those who require minimal supplemental oxygen) **(BIIa)**. In these individuals, the hyperinflammatory state where corticosteroids might be most beneficial may not yet be present or fully developed. For more information, please see Table 2a.

Rationale for the Use of Remdesivir Plus Dexamethasone

The safety and efficacy of using remdesivir plus dexamethasone for the treatment of COVID-19 have not been rigorously evaluated in clinical trials. Despite the lack of clinical trial data, there is a theoretical rationale for combining remdesivir and dexamethasone. 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. However, the data on clinical outcomes for patients who received this combination are currently limited.[5]

Based on the theoretical benefits of combining antiviral and anti-inflammatory effects, the Panel recommends the combination of **dexamethasone plus remdesivir** as a treatment option for patients in this group (e.g., those who require increasing amounts of supplemental oxygen) **(BIII)**.

Rationale for the Use of Dexamethasone

In the RECOVERY trial, treatment with dexamethasone conferred a survival benefit among participants who required supplemental oxygen at enrollment. Among these participants, fewer participants 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 participants were receiving and the proportions of participants who required oxygen through a high-flow device or noninvasive ventilation were not reported. It is possible that the benefit of dexamethasone was greatest in those who required more respiratory support. It should be noted that <0.1% of patients in the RECOVERY trial received concomitant remdesivir. See the Corticosteroids section for more information.

Some experts prefer not to use dexamethasone monotherapy in this group 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.[6-8] Some studies have suggested that corticosteroids slow SARS-CoV-2 clearance, but the results to date are inconclusive.[9-13]

Rationale for the Panel's Assessment That There Is Insufficient Evidence to Determine Which Patients Would Benefit from Dexamethasone Plus Baricitinib or Tocilizumab

In the COV-BARRIER trial (a multinational, placebo-controlled randomized trial), 1,525 hospitalized patients with COVID-19 with evidence of pneumonia, an elevation in one or more inflammatory markers, and an estimated glomerular filtration rate >30 mL/min/1.73 m^2 were randomized 1:1 to receive oral baricitinib 4 mg or placebo in addition to the local standard of care.[14] There was no significant difference between the study arms in the primary endpoint of the trial, the proportion of patients who progressed to requiring high-flow oxygen, noninvasive ventilation, invasive mechanical ventilation or death by Day 28. In the subgroup of patients who required supplemental oxygen but not a high-flow device or mechanical ventilation (n = 962), 28-day mortality was lower in the baricitinib arm than in the placebo arm (HR 0.72; 95% CI, 0.45–1.16; $P = 0.11$); however, this difference was not statistically significant.

Early trials that evaluated the use of tocilizumab in patients who were hospitalized with COVID-19 did not show a treatment effect for tocilizumab. These trials included a high proportion of patients receiving oxygen therapy; however, many of these trials were underpowered, and only a small proportion of patients were also receiving corticosteroids.[15-19] Although the RECOVERY trial reported a mortality benefit for tocilizumab, the study did not identify a particular subgroup of hospitalized patients on oxygen therapy who benefited most from receiving the drug.[20] Among 21,550 participants randomized into the RECOVERY trial, only 4,116 of the participants (19%) were preferentially selected for enrollment and randomization for the tocilizumab study, suggesting that the study results may not be generalizable to most hospitalized patients.

The Panel recognizes that there may be some hospitalized patients receiving oxygen therapy who may have progressive hypoxemia associated with significant systemic inflammation. The addition of baricitinib or tocilizumab to their standard treatment may provide a modest benefit; however, there is insufficient evidence to clearly characterize the subgroups within this patient population who would benefit from these interventions. As there are no studies that directly compare using baricitinib and tocilizumab as treatments for COVID-19, the Panel has insufficient evidence to recommend one drug over the other. Treatment decisions should be made based on local guidance, drug availability, and patient comorbidities.

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

Recommendations

- The Panel recommends one of the following options for these patients:
  - **Dexamethasone (AI)**; *or*
  - **Dexamethasone plus remdesivir (BIII)**.
- For recently hospitalized patients (i.e., those within 3 days of hospital admission) who have rapidly increasing oxygen needs, require high-flow oxygen or noninvasive ventilation, and have increased markers of inflammation, add **baricitinib (BIIa)** or **tocilizumab (BIIa)** (drugs are listed alphabetically and not in order of preference) to one of the two options above.
- 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.

Additional Considerations

- 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.[21,22] Many clinicians would initiate empiric treatment for strongyloidiasis (e.g., with ivermectin) with or without serologic testing in patients from areas where *Strongyloides* is endemic (i.e., tropical, subtropical, or warm temperate areas).

Using Other Corticosteroids

- If dexamethasone is not available, equivalent doses of other corticosteroids, such as **prednisone**, **methylprednisolone**, or **hydrocortisone**, may be used **(BIII)**. See Corticosteroids for more information.

Using Baricitinib and Tocilizumab

- Baricitinib or tocilizumab should only be given in combination with dexamethasone or another corticosteroid. Some clinicians may choose to 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, the Panel has insufficient evidence to recommend one drug over the other. Treatment decisions should be made based on local guidance, drug availability, and patient comorbidities.
- Although approximately a third of patients in the REMAP-CAP and RECOVERY trials received a second dose of tocilizumab at the discretion of their treating physicians, data on outcomes based on receipt of one or two 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 the Use of Dexamethasone

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

Rationale for the Use of Remdesivir Plus Dexamethasone

The combination of remdesivir plus dexamethasone has not been rigorously studied in clinical trials; therefore, the safety and efficacy of this combination are unknown. The Panel recognizes that there are theoretical reasons to use this combination, as described above. Based on these theoretical considerations, the Panel considers the combination of dexamethasone plus remdesivir a treatment option for patients in this group.

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 groups (recovery rate ratio 1.09; 95% CI, 0.76–1.57) in the subgroup of participants who required high-flow oxygen or noninvasive ventilation at enrollment (n = 193). A post hoc analysis did not show a survival benefit for remdesivir at Day 29, but the trial was not powered to detect this difference.[2] The Panel **does not recommend** using **remdesivir monotherapy** in these patients because there is uncertainty regarding whether remdesivir alone confers a clinical benefit in this subgroup **(AIIa)**. Dexamethasone or remdesivir plus dexamethasone are better treatment options for COVID-19 in this group of patients.

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

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

In the COV-BARRIER trial, 1,525 hospitalized patients with COVID-19 and an elevation of one or more inflammatory biomarkers were randomized 1:1 to receive oral baricitinib 4 mg or placebo in addition to the local standard of care for up to 14 days (or until hospital discharge).[14]

There was no difference in the primary endpoint of progression to high-flow oxygen, noninvasive ventilation, invasive 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; $P = 0.18$). 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 baricitinib (HR 0.57; 95% CI, 0.41–0.78; nominal $P = 0.002$). Across all the prespecified baseline disease severity subgroups, mortality estimates were numerically lower among those who received baricitinib than among those who received placebo. The difference in mortality was most pronounced in the subgroup of 370 patients receiving high-flow oxygen or noninvasive ventilation at baseline (17.5% of patients died 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 venous thromboembolic events was comparable in the arms.

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 noninvasive ventilation. Although people who were receiving corticosteroids were excluded from the ACTT-2 trial, the study results support that baricitinib may have a clinical benefit among patients with severe COVID-19 who are not able to receive corticosteroids.[23]

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

The REMAP-CAP and RECOVERY trials, the two largest randomized controlled tocilizumab trials 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 noninvasive ventilation.[20,24] Corticosteroids were given to most patients in both studies.

In the REMAP-CAP trial, patients admitted to an intensive care unit (ICU) with severe to critical COVID-19 and rapid respiratory decompensation were randomized to receive open-label tocilizumab or usual care. Compared to usual care, the use of tocilizumab reduced in-hospital mortality (28% vs. 36%) and, over 21 days of follow-up, increased the median number of days free of respiratory and cardiovascular organ support (10 days vs. 0 days; 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 the benefit of tocilizumab occurs in patients experiencing rapid respiratory decompensation. The evidence for therapeutic benefit was stronger among recipients who had recently started receiving oxygen through a high-flow device or noninvasive ventilation than among those who were already on mechanical ventilation; however, the lack of a formal subgroup analyses by oxygen requirement is a notable limitation of this study.

The RECOVERY trial also suggested a mortality benefit for tocilizumab plus dexamethasone in patients who specifically required noninvasive ventilation or high-flow oxygen. In this study, a subset of participants with hypoxemia and C-reactive protein levels ≥75 mg/L were randomized to receive tocilizumab or usual care. Tocilizumab reduced all-cause mortality in these patients; by Day 28, 29% of participants in the tocilizumab arm had died compared to 33% in the usual care arm (rate ratio 0.86; 95% CI, 0.77–0.96).

The Panel recommends the use of tocilizumab with concomitant corticosteroids **(BIIa)**, as multiple trials have reported that the clinical benefit of tocilizumab is seen among patients who are receiving tocilizumab plus corticosteroids (see Table 4d).

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 **(AIII)**, because there is insufficient evidence for the use of this combination. 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 duration of organ support was similar. Compared to noncontemporary control patients who received placebo plus dexamethasone, patients who received sarilumab and dexamethasone demonstrated reduced mortality, shorter time to ICU discharge, and more organ support-free days.[25]

In this study, sarilumab in combination with dexamethasone (n = 483) was noninferior to tocilizumab with dexamethasone (n = 943) with regards to the number of organ support-free days and mortality with a probability of 99% and 98%, respectively.

Even though the REMAP-CAP trial supports that sarilumab and tocilizumab have similar efficacy in the treatment of hospitalized patients with COVID-19, the Panel recommends **sarilumab** only when

tocilizumab is not available or is not feasible to use **(BIIa)**. The rationales for this recommendation are:

- The evidence for the efficacy of tocilizumab is more extensive than that for sarilumab, *and*
- Currently, sarilumab is only approved as a subcutaneous (SQ) injection in the United States.

In the REMAP-CAP trial, a single dose of sarilumab 400 mg for SQ injection was reconstituted in 50 ml or 100 ml of normal saline and administered as an intravenous 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, placebo-controlled randomized 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 occurred among 2.8% of the participants 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 participants in each arm also received corticosteroids. Serious adverse events occurred in 14.2% of the participants in the tofacitinib group and in 12.0% in the placebo group.[26]

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

Patients Who Require Invasive Mechanical Ventilation or Extracorporeal Membrane Oxygenation

Recommendations

- The Panel recommends the use of **dexamethasone** in hospitalized patients with COVID-19 who require invasive mechanical ventilation or ECMO **(AI)**.
- The Panel recommends the use of **dexamethasone plus tocilizumab** for patients who are within 24 hours of admission to the ICU **(BIIa)**.

Additional Considerations

- If dexamethasone is not available, equivalent doses of alternative corticosteroids (e.g., **prednisone**, **methylprednisolone**, **hydrocortisone**) may be used **(BIII)**.
- For patients who initially received remdesivir monotherapy and progressed to requiring invasive mechanical ventilation or ECMO, dexamethasone should be initiated and remdesivir should be continued until the treatment course is completed.
- The Panel **recommends against** the use of **remdesivir monotherapy (AIIa)**.
- 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 physicians, there is insufficient evidence to determine which patients, if any, would benefit from an additional dose of the drug.
- 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 ivermectin) should be considered for patients who are from areas where *Strongyloides* is endemic.

Rationale for the Use of Dexamethasone Monotherapy

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

Dexamethasone reduces mortality in critically ill patients with COVID-19 according to a meta-analysis that aggregated seven randomized trials and included data on 1,703 critically ill patients.[27] 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 the Corticosteroids section and Table 4a. Because the benefits outweigh the potential harms, the Panel recommends the use of **dexamethasone** in hospitalized patients with COVID-19 who require invasive mechanical ventilation or ECMO **(AI)**.

Considerations Related to the Use of Dexamethasone Plus Remdesivir Combination Therapy

Dexamethasone plus remdesivir combination therapy has not been evaluated in controlled studies; therefore, there is insufficient information to make a recommendation either for or against the use of this combination therapy. There is, however, a theoretical reason to administer dexamethasone plus remdesivir 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.[6,7]

Some studies have suggested that corticosteroids slow SARS-CoV-2 clearance, but the studies to date are not definitive. For example, an observational study in people with non-severe COVID-19 suggested that viral clearance was delayed in patients who received corticosteroids,[28] 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.[13] Given the conflicting results from observational studies and the absence of clinical trial data, some Panel members would coadminister **dexamethasone and remdesivir** in patients who have recently been placed on mechanical ventilation **(CIII)** until more conclusive evidence becomes available, based on their concerns about delayed viral clearance in patients who received corticosteroids. Other Panel members would not coadminister these drugs due to uncertainties about the benefit of using remdesivir in critically ill patients.

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 two largest randomized controlled tocilizumab trials to date, both reported a mortality benefit for tocilizumab among patients who experienced rapid respiratory decompensation and were recently admitted to the ICU, including those who required invasive mechanical ventilation.[20,24] The REMAP-CAP trial enrolled patients within 24 hours of admission to the ICU. Prior 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 4d). Thus, it is unclear whether there is a clinical benefit for tocilizumab in patients who received invasive 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 invasive mechanical ventilation. Please see the Rationale for Recommending the Use of Tocilizumab Plus Dexamethasone in Certain Hospitalized Patients section above for additional details on the clinical trial data and rationale for using tocilizumab in this situation.

Rationale for Recommending Against the Use of Remdesivir Monotherapy

A clear benefit of remdesivir monotherapy has not been demonstrated in patients who require invasive mechanical ventilation or ECMO. During the ACTT-1 trial, remdesivir did not improve the recovery rate in this subgroup of participants (recovery rate ratio 0.98; 95% CI, 0.70–1.36), and in a post hoc analysis of deaths by Day 29, remdesivir did not improve survival among 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 invasive mechanical ventilation or ECMO, the Panel recommends initiating dexamethasone and continuing remdesivir until the treatment course is completed. Clinical trials that evaluated remdesivir categorized patients based on their severity of illness at 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 Delivery of Oxygen Through a High-Flow Device or Noninvasive Ventilation but Not Invasive Mechanical Ventilation or Extracorporeal Membrane Oxygenation section above for the rationale regarding the use of sarilumab and dexamethasone as an alternative to tocilizumab and dexamethasone in certain hospitalized patients.

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Care of Critically Ill Adult Patients With COVID-19

Last Updated: July 8, 2021

Summary Recommendations

Infection Control

- For health care workers who are performing aerosol-generating procedures on patients with COVID-19, the COVID-19 Treatment Guidelines Panel (the Panel) recommends using an N95 respirator (or equivalent or higher-level respirator) rather than surgical masks, in addition to other personal protective equipment (PPE) (i.e., gloves, gown, and eye protection such as a face shield or safety goggles) **(AIII)**.
- The Panel recommends minimizing the use of aerosol-generating procedures on intensive care unit patients with COVID-19 and carrying out any necessary aerosol-generating procedures in a negative-pressure room, also known as an airborne infection isolation room, when available **(AIII)**.
- For health care workers who are providing usual care for nonventilated patients with COVID-19, the Panel recommends using an N95 respirator (or equivalent or higher-level respirator) or a surgical mask in addition to other PPE (i.e., gloves, gown, and eye protection such as a face shield or safety goggles) **(AIIa)**.
- For health care workers who are performing non-aerosol-generating procedures on patients with COVID-19 who are on closed-circuit mechanical ventilation, the Panel recommends using an N95 respirator (or equivalent or higher-level respirator) in addition to other PPE (i.e., gloves, gown, and eye protection such as a face shield or safety goggles) because ventilator circuits may become disrupted unexpectedly **(BIII)**.
- The Panel recommends that endotracheal intubation in patients with COVID-19 be performed by health care providers with extensive airway management experience, if possible **(AIII)**.
- The Panel recommends that intubation be performed using video laryngoscopy, if possible **(CIIa)**.

Hemodynamics

- For adults with COVID-19 and shock, the Panel recommends using dynamic parameters, skin temperature, capillary refilling time, and/or lactate levels over static parameters to assess fluid responsiveness **(BIIa)**.
- For the acute resuscitation of adults with COVID-19 and shock, the Panel recommends using buffered/balanced crystalloids over unbalanced crystalloids **(BIIa)**.
- For the acute resuscitation of adults with COVID-19 and shock, the Panel **recommends against** the initial use of **albumin** for resuscitation **(BI)**.
- For adults with COVID-19 and shock, the Panel recommends **norepinephrine** as the first-choice 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 patients with sepsis or septic shock **(AI)**.
- When norepinephrine is available, the Panel **recommends against** using **dopamine** for 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 patients who show evidence of cardiac dysfunction and persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents **(BIII)**.
- The Panel recommends that all patients who require vasopressors have an arterial catheter placed as soon as practical, if resources are available **(BIII)**.
- For adults with refractory septic shock who have completed a course of corticosteroids to treat their COVID-19, the Panel recommends using low-dose corticosteroid therapy ("shock-reversal") over no corticosteroid therapy **(BIIa)**.

Oxygenation and Ventilation

- For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy, the Panel recommends high-flow nasal cannula (HFNC) oxygen over noninvasive positive pressure ventilation (NIPPV) **(BIIa)**.
- In the absence of an indication for endotracheal intubation, the Panel recommends a closely monitored trial of NIPPV

for adults with COVID-19 and acute hypoxemic respiratory failure and for whom HFNC is not available **(BIIa)**.

- For patients with persistent hypoxemia despite increasing supplemental oxygen requirements in whom endotracheal intubation is not otherwise indicated, the Panel recommends considering a trial of awake prone positioning to improve oxygenation **(CIIa)**.
- The Panel **recommends against** using awake prone positioning as a rescue therapy for refractory hypoxemia to avoid intubation in patients who otherwise meet the indications for intubation and mechanical ventilation **(AIII)**.
- If intubation becomes necessary, the procedure should be performed by an experienced practitioner in a controlled setting due to the enhanced risk of 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)**.
- 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 (NMBA) or continuous NMBA infusion to facilitate protective lung ventilation **(BIIa)**.
  - In the event of persistent patient-ventilator dyssynchrony, or in cases where a patient requires ongoing deep sedation, prone ventilation, or persistently high plateau pressures, the Panel recommends using a continuous NMBA infusion for up to 48 hours as long as patient anxiety and pain can be adequately monitored and controlled **(BIII)**.
- For mechanically ventilated adults with COVID-19, severe ARDS, and hypoxemia despite optimized ventilation and other rescue strategies:
  - The Panel recommends using recruitment maneuvers rather than not using recruitment maneuvers **(CIIa)**.
  - If recruitment maneuvers are used, the Panel **recommends against** using staircase (incremental PEEP) recruitment maneuvers **(AIIa)**.
  - The Panel recommends using an inhaled pulmonary vasodilator as a rescue therapy; if no rapid improvement in oxygenation is observed, the treatment should be tapered off **(CIII)**.

Acute Kidney Injury and Renal Replacement Therapy

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

Pharmacologic Interventions

- In patients with COVID-19 and severe or critical illness, there is insufficient evidence for the Panel to recommend either for or against empiric broad-spectrum antimicrobial therapy in the absence of another indication.
- If antimicrobials are initiated, the Panel recommends that their use should be reassessed daily 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 for patients with COVID-19 and refractory hypoxemia.

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

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

General Considerations

Last Updated: April 21, 2021

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

Guidance on diagnostic testing for SARS-CoV-2 can be found in the Testing for SARS-CoV-2 Infection section.

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

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

Comorbid Conditions

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

Bacterial Superinfection of COVID-19-Associated Pneumonia

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

Inflammatory Response Due to COVID-19

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

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

Multisystem Inflammatory Syndrome in Adults

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

MIS-A is defined by the following criteria:

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

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

COVID-19-Induced Cardiac Dysfunction, Including Myocarditis

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

Thromboembolic Events and COVID-19

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

Renal and Hepatic Dysfunction Due to COVID-19

Although SARS-CoV-2 is primarily a pulmonary pathogen, renal and hepatic dysfunction are consistently described in patients with severe COVID-19.[4] In one case series of patients with critical disease, >15% of the patients required continuous renal replacement therapy.[6] See the Acute Kidney Injury and Renal

Replacement Therapy section for a more detailed discussion.

Considerations in Children

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

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

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

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

Sedation Management in Patients With COVID-19

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

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

A. Assess, prevent, and manage pain;

B. Both spontaneous awakening and breathing trials;

C. Choice of analgesia and sedation;

D. Delirium: assess, prevent, and manage;

E. Early mobility and exercise; *and*

F. Family engagement and empowerment.

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

Post-Intensive Care Syndrome

Patients with COVID-19 are reported to experience prolonged delirium and/or encephalopathy. Risk factors that are associated with delirium include the use of mechanical ventilation; the use of restraints; the use of benzodiazepine, opioid, and vasopressor infusions; and the use of antipsychotics.[36,37] Neurological complications are associated with older age and underlying conditions, such as hypertension and diabetes mellitus.[38] Autopsy studies have reported both macrovascular and microvascular thrombosis, with evidence of hypoxic ischemia.[39] Adequate management requires careful attention to best sedation practices and vigilance in stroke detection.

Post-intensive care syndrome (PICS) is a spectrum of cognitive, psychiatric, and/or physical disability that affects survivors of critical illness and persists after a patient leaves the ICU.[40] 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.[41-43] Cognitive dysfunction affects 30% to 80% of patients discharged from the ICU.[44-46] About 50% of ICU survivors do not return to work within 1 year after discharge.[47] Although no single risk factor has been associated with PICS, there are opportunities to minimize the risk of PICS through medication management (using the A-F Bundle), physical rehabilitation, follow-up clinics, family support, and improved education about the syndrome. PICS also affects family members who participate in the care of their loved ones. In one study, a third of family members who had main decision-making roles experienced mental health problems, such as depression, anxiety, and PTSD.[48]

Early reports suggest that some patients with COVID-19 who have been treated in the ICU express manifestations of PICS.[49] Although specific therapies for COVID-19-induced PICS are not yet available, physicians should maintain a high index of suspicion for cognitive impairment and other related problems in survivors of severe or critical COVID-19 illness.

Other Intensive Care Unit-Related Complications

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

Advance Care Planning and Goals of Care

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

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

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

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Infection Control

Last Updated: October 9, 2020

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

Recommendation

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

Rationale

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

Recommendation

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

Rationale

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

Recommendations

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

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

Rationale

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

Recommendations

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

Rationale

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

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Hemodynamics

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

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 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

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The COVID-19 Treatment Guidelines Panel's (the Panel) recommendations in this section emphasize recommendations from the Surviving Sepsis Campaign Guidelines for managing adult sepsis, pediatric sepsis, and COVID-19.

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 uncertain. 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 <92% or >96% may be harmful.

The potential harm of maintaining an SpO_2 <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 ≥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 >96%. This study found that a liberal oxygen strategy (median SpO_2 of 96%) was associated with an increased risk of in-hospital mortality when compared to a more conservative SpO_2 strategy (relative risk 1.21; 95% CI, 1.03–1.43).[2]

Acute Hypoxemic Respiratory Failure

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

Nonmechanically Ventilated Adults With Acute Hypoxemic Respiratory Failure

High-Flow Nasal Cannula Oxygen and Noninvasive Positive Pressure Ventilation

Recommendations

- For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy, the Panel recommends HFNC oxygen over NIPPV **(BIIa)**.
- For adults with COVID-19 and acute hypoxemic respiratory failure for whom HFNC oxygen is not available, in the absence of an indication for endotracheal intubation, the Panel recommends a closely monitored trial of NIPPV **(BIIa)**.

Rationale

HFNC oxygen is preferred over NIPPV in patients with acute hypoxemic respiratory failure; 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 NIPPV. The patients in the HFNC oxygen arm had more ventilator-free days (mean 24 days) than those in the conventional oxygen therapy arm (mean 22 days) or NIPPV arm (19 days; $P = 0.02$). In addition, 90-day mortality was lower in the HFNC oxygen arm than in either the conventional oxygen therapy arm (HR 2.01; 95% CI, 1.01–3.99) or the NIPPV arm (HR 2.50; 95% CI, 1.31–4.78).[3] In the subgroup of more severely hypoxemic patients (those with a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen [PaO_2/FiO_2] mm Hg ≤200), the intubation rate was lower for the HFNC oxygen arm than for the conventional oxygen therapy or NIPPV arms (HR 2.07 and 2.57, respectively).

The trial's findings were corroborated by a meta-analysis of eight trials with 1,084 participants that was conducted to assess the effectiveness of oxygenation strategies prior to intubation. Compared to NIPPV, 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]

NIPPV is an aerosol-generating procedure, and it may increase the risk of nosocomial transmission of SARS-CoV-2.[5,6] It remains unclear whether the use of HFNC oxygen results in a lower risk of nosocomial SARS-CoV-2 transmission than NIPPV.

Awake Prone Positioning in Nonmechanically Ventilated Adults

Recommendations

- For patients 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** using awake prone positioning as a rescue therapy for refractory hypoxemia to avoid intubation in patients who otherwise meet the indications for intubation and invasive mechanical ventilation **(AIII)**.

Additional Considerations

- Appropriate candidates for awake prone positioning are those who can adjust their position independently and tolerate lying prone.
- 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.[7]
- Some patients do not tolerate awake prone positioning. Failure rates as high as 63% have been reported in the literature.[8]
- Awake proning **should not be used** as a substitute for intubation and invasive mechanical ventilation in patients with refractory hypoxemia who otherwise meet the indications for these interventions.
- Awake proning 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 or delirium, hemodynamic instability, an inability to independently change position, recent abdominal surgery, or recent nausea or vomiting.[9]

Rationale

Awake proning, or having a nonintubated patient lie on their stomach, may improve oxygenation and prevent the patient from progressing to requiring invasive mechanical ventilation. Although prone positioning has been shown to improve oxygenation and outcomes in patients with moderate to severe ARDS who are receiving invasive mechanical ventilation,[10,11] 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 NIPPV have similarly reported that awake prone positioning improves oxygenation,[12-15] and some series have also reported low intubation rates after proning.[12,14]

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 six 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; the intention-to-treat analysis included 1,121 patients. Two hundred twenty-three of 564 patients (40%) who underwent awake prone positioning met the primary composite outcome 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 at 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 occurred more frequently in patients who experienced 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 two arms. No cardiac arrests occurred during awake prone positioning.[16]

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.[10,11]

Intubation for Invasive 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 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 Acute Respiratory Distress Syndrome

Recommendations

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

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

Rationale

PEEP is beneficial in patients with ARDS because it prevents alveolar collapse, improves oxygenation, and minimizes atelectotrauma, a source of ventilator-induced lung injury. A meta-analysis of individual patient data from the three largest trials that compared lower and higher levels of PEEP in patients without COVID-19 found lower rates of ICU mortality and in-hospital mortality with higher 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).[17]

Although there is no clear standard as to what constitutes a high level of PEEP, one conventional threshold is >10 cm H_2O.[18] 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.[19,20] Other studies 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.[21-24] These seemingly contradictory observations suggest that COVID-19 patients with ARDS are a heterogeneous population, and assessment 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.

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

Recommendations

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

- The Panel recommends using, as needed, intermittent boluses of neuromuscular blocking agents (NMBA) or 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 patient anxiety and pain can be adequately monitored and controlled **(BIII)**.

Rationale

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

Rescue Therapies for Mechanically Ventilated Adults With Acute Respiratory Distress Syndrome

Recommendations

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

- The Panel recommends using recruitment maneuvers rather than not using recruitment maneuvers **(CIIa)**.
- If recruitment maneuvers are used, the Panel **recommends against** using staircase (incremental PEEP) recruitment maneuvers **(AIIa)**.
- The Panel recommends using an inhaled pulmonary vasodilator as a rescue therapy; if no rapid improvement in oxygenation is observed, the treatment should be tapered off **(CIII)**.

Rationale

No studies have assessed the effect of recruitment maneuvers on oxygenation in severe ARDS due to COVID-19. However, a systematic review and meta-analysis of six trials of recruitment maneuvers in 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.[25] Because recruitment maneuvers can cause barotrauma or hypotension, patients should be closely monitored during recruitment maneuvers. If a patient decompensates during recruitment maneuvers, the maneuver should be stopped immediately. The importance of properly performing recruitment maneuvers was illustrated by an analysis of eight randomized controlled trials in 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). Subgroup analysis found that traditional recruitment maneuvers significantly reduced hospital mortality (risk ratio 0.85; 95% CI, 0.75–0.97), whereas incremental PEEP titration recruitment maneuvers increased mortality (risk ratio 1.06; 95% CI, 0.97–1.17).[26]

Although there are no published studies of inhaled nitric oxide in patients with COVID-19, a Cochrane review of 13 trials of inhaled nitric oxide use in patients with ARDS found no mortality benefit.[27]

Because the review showed a transient benefit in oxygenation, it is reasonable to attempt using inhaled nitric oxide as a rescue therapy in COVID patients with severe ARDS after other options have failed. However, if there is no benefit in oxygenation with inhaled nitric oxide, it should be tapered quickly to avoid rebound pulmonary vasoconstriction that may occur with discontinuation after prolonged use.

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Acute Kidney Injury and Renal Replacement Therapy

Last Updated: December 17, 2020

Recommendations

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

Rationale

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

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

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

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Pharmacologic Interventions

Last Updated: July 8, 2021

Therapeutic Management of Adults with COVID-19

See Therapeutic Management of Hospitalized Adults with COVID-19 for the COVID-19 Treatment Guidelines Panel's (the Panel) recommendations on when to use the following drugs alone or in combination: baricitinib, dexamethasone, remdesivir, and tocilizumab.

Immune-Based Therapy

See the Immunomodulators sections for additional recommendations regarding the use of immunomodulators not listed above.

Adjunctive Therapy

Recommendations regarding adjunctive therapy in the critical care setting, including antithrombotic therapy and vitamin C, can be found in Antithrombotic Therapy in Patients With COVID-19 and in the Supplements sections.

Empiric Broad-Spectrum Antimicrobial Therapy

Recommendations

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

Rationale

At this time, there are no reliable estimates of the incidence or prevalence of copathogens with SARS-CoV-2.

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

Gram stain, culture, or other testing of respiratory specimens is often not available due to concerns about aerosolization of SARS-CoV-2 during diagnostic procedures or when processing specimens.

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

Extracorporeal Membrane Oxygenation

Last Updated: December 17, 2020

Recommendation

- There is insufficient evidence 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] A recent case series of 83 COVID-19 patients in Paris reported a 60-day mortality of 31% for patients on ECMO.[8] This mortality was similar to the mortality observed in a 2018 study of non-COVID-19 patients with ARDS who were treated with ECMO during the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial; that study reported a mortality of 35% at Day 60.[3]

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

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

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

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

Last Updated: July 8, 2021

Summary Recommendations
Remdesivir is the only Food and Drug Administration-approved drug for the treatment of COVID-19. In this section, the COVID-19 Treatment Guidelines Panel (the Panel) provides recommendations for using antiviral drugs to treat COVID-19 based on the available data. **As in the management of any disease, treatment decisions ultimately reside with the patient and their health care provider.** For more information on these antiviral agents, see Table 2e. **Remdesivir** • See Therapeutic Management of Hospitalized Adults with COVID-19 for recommendations on using remdesivir with or without dexamethasone. **Ivermectin** • There is insufficient evidence for the Panel to recommend either for or against the use of ivermectin for the treatment of COVID-19. Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of ivermectin in the treatment of COVID-19. **Nitazoxanide** • The Panel **recommends against** the use of **nitazoxanide** for the treatment of COVID-19, except in a clinical trial **(BIIa)**. **Hydroxychloroquine or Chloroquine and/or Azithromycin** • 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)**. **Lopinavir/Ritonavir and Other HIV Protease Inhibitors** • The Panel **recommends against** the use of **lopinavir/ritonavir** and **other HIV protease inhibitors** for the treatment of COVID-19 in hospitalized patients **(AI)** and in nonhospitalized patients **(AIII)**.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional **Rating of Evidence:** I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

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

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

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Remdesivir

Last Updated: April 21, 2021

Remdesivir is an intravenous nucleotide prodrug of an adenosine analog. Remdesivir binds to the viral RNA-dependent RNA polymerase and inhibits viral replication through premature termination of RNA transcription. It 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 approved by the Food and Drug Administration (FDA) for the treatment of COVID-19 in hospitalized adult and pediatric patients (aged ≥12 years and weighing ≥40 kg). It is also available through an FDA Emergency Use Authorization (EUA) for the treatment of COVID-19 in hospitalized pediatric patients weighing 3.5 kg to <40 kg or aged <12 years and weighing ≥3.5 kg. Remdesivir should be administered in a hospital or a health care setting that can provide a similar level of care to an inpatient hospital.

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

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

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.

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

Considerations in Patients With Renal Insufficiency

Each 100 mg vial of remdesivir lyophilized powder contains 3 g of sulfobutylether beta-cyclodextrin sodium (SBECD), whereas each 100 mg/20 mL vial of remdesivir solution contains 6 g of SBECD.[3] 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.[4] 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 estimated glomerular filtration rate (eGFR) of <50 mL/min were excluded from some clinical trials of remdesivir; other trials had an eGFR cutoff of <30 mL/min. Remdesivir **is not recommended** for patients with an eGFR <30 mL/

min due to lack of data.[5] Renal function should be monitored before and during remdesivir treatment as clinically indicated.[3]

In two observational studies that evaluated the use of remdesivir 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) <30 mL/min and those with an estimated CrCl ≥30 mL/min.[6,7] One of these studies evaluated patients who primarily received the solution formulation of remdesivir (20 patients had an estimated CrCl <30 mL/min and 115 had an estimated CrCl ≥30 mL/min);[6] the other study evaluated patients who received the lyophilized powder formulation (40 patients had an estimated CrCl <30 mL/min and 307 had an estimated CrCl ≥30 mL/min).[7]

Drug-Drug Interactions

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

Minimal to no reduction in remdesivir exposure is expected when remdesivir is coadministered with dexamethasone, according to information provided by Gilead Sciences (written communication, July 2020). Chloroquine or hydroxychloroquine may decrease the antiviral activity of remdesivir; coadministration of these drugs **is not recommended**.[3] Remdesivir is not expected to have any significant interactions with oseltamivir or baloxavir, according to information provided by Gilead Sciences (written communications, August and September 2020).

See Table 2e for more information.

Considerations in Pregnancy

- Pregnant patients were excluded from the clinical trials that evaluated the safety and efficacy of remdesivir for the treatment of COVID-19, but preliminary reports of remdesivir use in pregnant patients from the remdesivir compassionate use program are reassuring.
- Among 86 pregnant and postpartum hospitalized patients with severe COVID-19 who received compassionate use remdesivir, the therapy was well tolerated, with a low rate of serious adverse events.[8]
- Remdesivir should not be withheld from pregnant patients if it is otherwise indicated.

Considerations in Children

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

Clinical Trials

Several clinical trials that are evaluating 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

Last Updated: February 11, 2021

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

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

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

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

Study Design	Methods	Results	Limitations and Interpretation
World Health Organization Solidarity Trial[3], continued			
	Primary Endpoint: • In-hospital mortality **Secondary Endpoints:** • Initiation of mechanical ventilation • Duration of hospitalization	• Percentage of patients hospitalized for ≥2 days at entry: 40% in RDV arm, 39% in SOC arm • Percentages of patients with comorbid conditions were similar between RDV and SOC arms: diabetes (26% and 25%), heart disease (21% both groups), and chronic lung disease (6% and 5%). • 48% of patients in both arms received corticosteroids. **Primary Outcomes:** • In-hospital mortality: 301 deaths (11.0%) in RDV arm, 303 deaths (11.2%) in SOC arm • Rate ratios for in-hospital death: • Overall: 0.95 (95% CI, 0.81–1.11) • No mechanical ventilation at entry: 0.86 (99% CI, 0.67–1.11) • Mechanical ventilation at entry: 1.20 (99% CI, 0.80–1.80) **Secondary Outcomes:** • Initiation of mechanical ventilation: 295 patients (10.8%) in RDV arm, 284 patients (10.5%) in SOC arm	**Interpretation:** • RDV did not decrease in-hospital mortality in hospitalized patients when compared to local SOC.
Remdesivir Versus Standard of Care in Hospitalized Patients with Moderate COVID-19[4]			
Open-label randomized trial in hospitalized patients (n = 596)	**Key Inclusion Criteria:** • Laboratory-confirmed SARS-CoV-2 infection • Moderate pneumonia, defined as radiographic evidence of pulmonary infiltrates and SpO_2 >94% on room air **Key Exclusion Criteria:** • ALT or AST >5 times ULN • CrCl <50 mL/min	**Number of Participants:** • 584 patients began treatment: 10-day RDV (n = 193), 5-day RDV (n = 191), and SOC (n = 200) **Participant Characteristics:** • Demographic and baseline disease characteristics were similar across all arms. **Outcomes:** • 5-day RDV had significantly higher odds of better clinical status distribution on Day 11 than SOC (OR 1.65; 95% CI, 1.09–2.48; *P* = 0.02).	**Limitations:** • Open-label design may have affected decisions related to concomitant medication use and hospital discharge. • Greater proportion of patients in SOC arm received HCQ, LPV/RTV, or AZM, which may cause AEs and have not shown clinical benefits in hospitalized patients with COVID-19.

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

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

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

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Chloroquine or Hydroxychloroquine 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 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 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.

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.

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.

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

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.

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.

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 log10 copies/mL; difference of -0.07; 95% CI, -0.44 to 0.29). • No difference in the risk of hospitalization between control arm and HCQ arm (7.1% vs. 5.9%; risk ratio 0.75; 95% CI, 0.32–1.77) • No difference in the median time from randomization to the resolution of COVID-19 symptoms between the 2 arms (12.0 days in control arm vs. 10.0 days in HCQ arm; *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.

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.

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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Ivermectin

Last Updated: February 11, 2021

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

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

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

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

Recommendation

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

Rationale

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

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

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

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

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

Monitoring, Adverse Effects, and Drug-Drug Interactions

- Ivermectin is generally well tolerated. Adverse effects may include dizziness, pruritis, nausea, or diarrhea.
- Neurological adverse effects have been reported with the use of ivermectin for the treatment of onchocerciasis and other parasitic diseases, but it is not clear whether these adverse effects were caused by ivermectin or the underlying conditions.[28]
- Ivermectin is a minor cytochrome P 3A4 substrate and a p-glycoprotein substrate.
- Ivermectin is generally given on an empty stomach with water; however, administering ivermectin with food increases its bioavailability.
- The FDA issued a warning in April 2020 that ivermectin intended for use in animals **should not be used** to treat COVID-19 in humans.
- Please see Table 2c for additional information.

Considerations in Pregnancy

In animal studies, ivermectin was shown to be teratogenic when given in doses that were maternotoxic. These results raise concerns about administering ivermectin to people who are in the early stages of pregnancy (prior to 10 weeks gestation).[29] A 2020 systematic review and meta-analysis reviewed the incidence of poor maternal and fetal outcomes after ivermectin was used for its antiparasitic properties during pregnancy. However, the study was unable to establish a causal relationship between ivermectin use and poor maternal or fetal outcomes due to the quality of evidence. There are numerous reports of inadvertent ivermectin use in early pregnancy without apparent adverse effects.[30-32] Therefore, there is insufficient evidence to establish the safety of using ivermectin in pregnant people, especially those in the later stages of pregnancy.

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

Considerations in Children

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

Clinical Trials

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

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Table 2c. Ivermectin: Selected Clinical Data

Last Updated: July 19, 2021

The Panel has reviewed other clinical studies of IVM for the treatment of COVID-19.[1-16] However, those studies have limitations that make them less definitive and informative than the studies discussed here. The studies summarized below are those that have had the greatest impact on the Panel's recommendations.

Study Design	Methods	Results	Limitations and Interpretation
Ivermectin Versus Placebo for Treatment of Mild COVID-19[17]			
Randomized, double-blind, placebo-controlled trial in Cali, Colombia (n = 476)	**Key Inclusion Criteria:** • Positive SARS-CoV-2 PCR result or positive antigen test result • Symptoms began ≤7 days prior to randomization • Mild disease (defined as receiving outpatient or inpatient care, but not receiving HFNC oxygen or mechanical ventilation) **Key Exclusion Criteria:** • Asymptomatic disease • Severe pneumonia • Receipt of IVM within previous 5 days • Hepatic dysfunction/abnormal liver function tests **Interventions:** • Oral IVM 300 μg/kg per day in solution for 5 days, taken primarily on an empty stomach • Placebo **Primary Endpoints:** • Time from randomization to resolution of symptoms within	**Number of Participants:** • IVM (n = 200) and placebo (n = 198) in primary analysis **Participant Characteristics:** • Median age was 37 years; 4% of patients in IVM arm and 8% in placebo arm were aged ≥65 years. • 39% of patients in IVM arm and 45% in placebo arm were male. • 79% of patients had no known comorbidities; median BMI in both arms was 26. • Median time from symptom onset to randomization was 5 days (IQR 4–6 days). • 62% of patients in IVM arm and 55% in placebo arm were not hospitalized and had no limitations of activities at baseline (ordinal scale 1); 38% and 44% were not hospitalized but had some limitations on activities, or they were receiving oxygen at home, or both (ordinal scale 2). • 1% of patients in both arms were hospitalized at baseline. **Primary Outcomes:** • No difference in time to resolution of symptoms (median 10 days in IVM arm vs. 12 days in placebo arm; HR 1.07; 95% CI, 0.87–1.32; $P = 0.53$) • Symptoms resolved in 82% of patients in IVM arm and 79% in placebo arm by Day 21. **Other Outcomes:** • No significant difference between arms in proportion of patients who showed clinical deterioration of ≥2 points on the ordinal scale (3.5% in IVM arm vs. 2.0% in placebo arm; absolute difference -1.5%; 95% CI, -4.8% to 1.7%)	**Key Limitations:** • Relatively small sample size • Primary endpoint was modified during the trial due to lower than expected event rates. • The first 65 patients received a placebo that smelled and tasted different from IVM. • The study enrolled a younger, healthier demographic than those who typically experience more serious cases of COVID-19. • Study included 4 hospitalized patients (out of 398). • The IVM dose used in this study was higher than the dose that is usually administered (IVM 200 μg/kg per day). **Interpretation:** • A 5-day course of IVM did not improve time to resolution of symptoms in patients with mild COVID-19.

Study Design	Methods	Results	Limitations and Interpretation
Ivermectin Versus Placebo for Treatment of Mild COVID-19[17], continued			
	the 21-day follow-up period. Resolution of symptoms was defined as the first day a patient reported a score of 0 (no clinical evidence of infection) on an 8-point ordinal scale.	• No significant difference between arms in the odds of improvement in ordinal scale score and the proportion of patients who sought medical care or required escalation in care. • 8% of patients in IVM arm and 3% in placebo arm discontinued treatment due to an AE. None of the reported SAEs were considered to be related to study interventions.	
Ivermectin Versus Ivermectin Plus Doxycycline Versus Placebo for Treatment of COVID-19[18]			
Randomized, double-blind, placebo-controlled trial of hospitalized adults in Dhaka, Bangladesh (n = 72)	**Key Inclusion Criteria:** • Aged 18–65 years • Laboratory-confirmed SARS-CoV-2 infection with fever, cough, or sore throat • Admitted to hospital within previous 7 days **Key Exclusion Criteria:** • Chronic cardiac, renal, or liver disease **Interventions:** • IVM 12 mg PO once daily for 5 days • Single dose of IVM 12 mg PO plus DOX 200 mg PO on Day 1, then DOX 100 mg every 12 hours for 4 days • Placebo **Primary Endpoints:** • Time to virologic clearance, measured by obtaining an NP swab for SARS-CoV-2 PCR on Days 3, 7, and 14, then weekly until PCR result was negative • Resolution of fever and cough within 7 days	**Number of Participants:** • IVM (n = 24; 2 withdrew), IVM plus DOX (n = 24; 1 withdrew), and placebo (n = 24; 1 withdrew) **Participant Characteristics:** • Mean age was 42 years. • 54% of patients were female. • Mean time from symptom onset to assessment was 3.83 days. • No patients required supplemental oxygen. **Primary Outcomes:** • Shorter mean time to virologic clearance with IVM than placebo (9.7 days vs. 12.7 days; $P = 0.02$), but not with IVM plus DOX (11.5 days; $P = 0.27$). • Rates of virologic clearance were greater in IVM arm at Day 7 (HR 4.1; 95% CI, 1.1–14.7; $P = 0.03$) and at Day 14 (HR 2.7; 95% CI, 1.2–6.0; $P = 0.02$) compared to placebo, but not in the IVM plus DOX arm (HR 2.3; 95% CI, 0.6–9.0; $P = 0.22$ and HR 1.7; 95% CI, 0.8–4.0; $P = 0.19$). • No statistically significant difference in time to resolution of fever, cough, or sore throat between IVM and placebo arms ($P = 0.35$, $P = 0.18$, and $P = 0.35$, respectively) or IVM plus DOX and placebo arms ($P = 0.09$, $P = 0.23$, and $P = 0.09$, respectively).	**Key Limitations:** • Small sample size • Unclear whether both IVM and DOX placebos were used. • Excluded patients with chronic diseases. • Disease appears to have been mild in all patients; thus, the reason for hospitalization is unclear. • Absolute changes in inflammatory markers were not presented, but were reportedly significant. • PCR results are not a validated surrogate marker for clinical efficacy. **Interpretation:** • A 5-day course of IVM resulted in faster virologic clearance than placebo, but not a faster time to resolution of symptoms (fever, cough, and sore throat).

Study Design	Methods	Results	Limitations and Interpretation
Ivermectin Versus Ivermectin Plus Doxycycline Versus Placebo for Treatment of COVID-19[18], continued			
		Other Outcomes: • Mean values of CRP, LDH, procalcitonin, and ferritin declined in all arms from baseline to Day 7, but there were no between-arm comparisons of the changes. • No between-arm differences in duration of hospitalization (P = 0.93). • No SAEs recorded.	Because time to virologic clearance is not a validated surrogate marker for clinical efficacy, the clinical efficacy of IVM is unknown.
Effectiveness and Safety of Adding Ivermectin to Treatment in Patients With Severe COVID-19[19]			
Randomized, single-blind trial of hospitalized adults in Turkey (n = 66)	**Key Inclusion Criteria:** • Hospitalized with PCR-confirmed SARS-CoV-2 infection • ≥1 of the following severity criteria: • Tachypnea (≥30 breaths/min), SpO_2 <90% on RA, or PaO_2/FiO_2 <300 mm Hg in patients who were receiving oxygen • Presence of "specific" radiologic findings • Mechanical ventilation • Acute organ dysfunction **Key Exclusion Criteria:** • Aged <18 years • Pregnant or breast feeding • Autoimmune disease • Chronic liver or kidney disease • Immunosuppression • SNP mutation in MDR1/ABCB1 gene and/or haplotypes and mutations of the CYP3A4 gene (affects IVM metabolism and toxicity)	**Number of Participants:** • IVM (n = 36) and SOC (n = 30) • 6 participants in IVM arm were excluded after genotyping. **Participant Characteristics:** • Mean age was 58 years in IVM arm and 66 years in SOC arm. • 70% of patients were male in IVM arm and 63% were male in SOC arm. • Comorbidities (IVM vs. SOC): DM (30% vs. 33%), HTN (50% vs. 40%), CAD (17% vs. 27%) **Primary Outcome:** • Clinical improvement at Day 5: 14 of 30 patients (46.7%) in IVM arm, 11 of 30 (36.7%) in SOC arm (P = 0.43) **Secondary Outcomes** *Between-Arm Comparisons at Day 10:* • Clinical improvement: 73.3% in IVM arm, 53.3% in SOC arm (P = 0.10) • IVM vs. SOC arm SOFA score at Day 10: P = 0.50 • Mean SpO_2: 95.4% in IVM arm, 93.0% in SOC arm (P = 0.032) • Mean PaO_2/FiO_2: 236.3 mm Hg in IVM arm, 220.8 mm Hg in SOC arm (P = 0.39) • Serum CRP, ferritin, and D-dimer levels were lower in IVM arm than in SOC arm (P = 0.02, P = 0.005, and P = 0.03, respectively).	**Key Limitations:** • Small sample size • Time from symptom onset to intervention was not reported. • Study used nonstandard severity classification for COVID-19. • Primary endpoint was difficult to characterize; it was presented in the Methods section as a composite endpoint, but each component was analyzed separately. • Power analysis performed for virologic endpoint, not primary endpoint. • Only 57% of patients in IVM arm and 27% in SOC arm were evaluated for VL changes. **Interpretation:** • A 5-day course of IVM in hospitalized patients with severe COVID-19 did not result in clinical improvement at the end of treatment, and no reduction in mortality was observed.

Study Design	Methods	Results	Limitations and Interpretation
Effectiveness and Safety of Adding Ivermectin to Treatment in Patients With Severe COVID-19[19], continued			
	Interventions: • IVM 200 µg/kg per day for 5 days plus SOC (HCQ plus favipiravir plus AZM) • SOC alone **Primary Endpoint:** • “Clinical response” at Day 5: extubation (in mechanically ventilated patients), respiratory rate <26 breaths/min, SpO_2 >90% on RA, PaO_2/FiO_2 >300 mm Hg (if patient was receiving oxygen), presence of ≥2 of the 2-point reduction criteria in SOFA **Key Secondary Endpoints:** • Clinical response at Day 10: respiratory rate 22 to 24 breaths/min, SpO_2 >95% on RA, absence of oxygen requirement, and no need for intensive care • Changes in SpO_2, PaO_2/FiO_2, and levels of CRP, ferritin, and D-dimer • Mortality	*Within-Group Changes from Baseline:* • Change in SOFA score to Day 10: P = 0.009 in IVM arm, P = 0.88 in SOC arm • Mean changes in SpO_2 to Day 5: 89.9% to 93.5% (P = 0.005) in IVM arm, 89.7% to 93.0% (P = 0.003) in SOC arm *Mortality During Follow-Up Period:* • 6 patients (20%) in IVM arm and 9 (30%) in SOC arm (P = 0.37). • Average length of follow-up was 3 months.	• Faster improvement of oxygenation and more pronounced reduction in inflammatory markers were observed in IVM arm.
Chloroquine, Hydroxychloroquine, or Ivermectin in Patients With Severe COVID-19[20]			
Randomized, double-blind, Phase 2 trial of hospitalized adults in Brazil (n = 168)	**Key Inclusion Criteria:** • Hospitalized with laboratory-confirmed SARS-CoV-2 infection (PCR or IgM positive) • ≥1 of the following severity criteria: • Dyspnea • Tachypnea (>30 breaths/min) • SpO_2 <93% • PaO_2/FiO_2 <300 mm Hg	**Number of Participants:** • CQ (n = 61), HCQ (n = 54), and IVM (n = 53) **Participant Characteristics:** • Mean age was 53.4±15.6 years. • 58.2% of patients were male. • 78.9% of patients were Hispanic. • 37.5% of patients had a BMI >30. • Most common comorbidities were HTN (43.4% of patients) and DM (28.1%).	**Key Limitations:** • Small sample size • No placebo control • No clear primary endpoint **Interpretation:** • Use of IVM did not reduce risk of oxygen requirement, ICU admission, invasive mechanical ventilation, or death in

Study Design	Methods	Results	Limitations and Interpretation
Chloroquine, Hydroxychloroquine, or Ivermectin in Patients With Severe COVID-19[20], continued			
	• Involvement of >50% of lungs on CXR or CT **Key Exclusion Criteria:** • Aged <18 years old • Cardiac arrhythmia, including prolonged QT interval • Previous use of CQ, HCQ, or IVM for >24 hours **Interventions:** • CQ 450 mg twice daily on Day 0, then CQ 450 mg once daily for 4 days • HCQ 400 mg twice daily on Day 0, then HCQ 400 mg once daily for 4 days • IVM 14 mg once daily for 3 days followed by placebo for 2 days **Endpoints:** • Need for supplemental oxygen, invasive mechanical ventilation, or ICU admission • Mortality	• On admission, 76.5% of patients had respiratory failure, and 42.5% had "pneumonic syndrome." **Outcomes:** • No differences between arms in proportion of patients who required supplemental oxygen (88.5% in CQ arm, 90.2% in HCQ arm, and 88.4% in IVM arm) or mean number of days of supplemental oxygenation (7.9 vs. 7.8 vs. 8.1 days) • No differences between arms in proportion of patients admitted to the ICU (22.4% in CQ arm, 21.1% in HCQ arm, and 28.0% in IVM arm) or proportion of patients who received invasive mechanical ventilation (20.6% vs. 21.1% vs. 23.5%) • No differences between arms in proportion of patients who were receiving concomitant medications, including steroids and anticoagulants • No differences between arms in death due to COVID-19 complications (21.3% in CQ arm, 22.2% in HCQ arm, and 23.0% in IVM arm) • Baseline characteristics that were associated with mortality included age >60 years (HR 2.44; 95% CI, 1.40–4.30), DM (HR 1.87; 95% CI, 1.02–2.59), BMI >33 (HR 1.95; 95% CI, 1.07–3.09), and SpO_2 <90% (HR 5.79; 95% CI, 2.63–12.7). • No difference in rates of AEs between arms	hospitalized patients with severe COVID-19.
Ivermectin Versus Placebo for Outpatients With Mild COVID-19[21]			
Open-label RCT of adult outpatients in Lahore, Pakistan (n = 50)	**Key Inclusion Criteria:** • SARS-CoV-2 PCR positive • Mild disease **Key Exclusion Criteria:** • Severe symptoms likely related to cytokine storm • Malignancy, chronic kidney disease, or cirrhosis • Pregnancy	**Number of Participants:** • IVM (n = 25) and control (n = 25) **Participant Characteristics:** • Mean age was 40.6 years. • 62% of patients were male. • 40% of patients had diabetes, 30% were smokers, 26% had hypertension, 8% had cardiovascular disease, and 12% had obesity.	**Key Limitations:** • Small sample size • Open-label study • Authors reported the proportions of patients with certain symptoms and comorbidities but did not provide objective assessment of disease severity. This precludes the ability to compare outcomes between arms.

Study Design	Methods	Results	Limitations and Interpretation
Ivermectin Versus Placebo for Outpatients With Mild COVID-19[21], continued			
	Interventions: • IVM 12 mg PO immediately, followed by 12 mg doses at 12 and 24 hours, plus symptomatic treatment • Symptomatic treatment **Primary Endpoint:** • Symptoms reported on Day 7. Patients were stratified as asymptomatic or symptomatic.	**Outcomes:** • Proportion of asymptomatic patients at Day 7 was similar in IVM and control arms (64% vs. 60%; *P* = 0.500). • AEs were attributed to IVM in 8 patients (32%).	• Study classified outcomes at Day 7 as "symptomatic" and "asymptomatic," but did not account for symptom worsening or improvement. **Interpretation:** • IVM showed no effect on symptom resolution in patients with mild COVID-19.
Ivermectin in Patients With Mild to Moderate COVID-19[22]			
Open-label, single-center, RCT of outpatients with laboratory-confirmed SARS-CoV-2 infection in Bangladesh (n = 62)	**Key Inclusion Criteria:** • Aged ≥18 years • Laboratory-confirmed SARS-CoV-2 infection • ≤7 days of symptoms • Mild or moderate disease **Key Exclusion Criteria:** • Hypersensitivity to IVM • Pregnancy or breastfeeding • Use of HCQ or "other antimicrobials" **Interventions:** • Single dose of IVM 200 µg/kg • SOC **Primary Endpoint:** • Full recovery from all symptoms **Secondary Endpoint:** • Conversion to negative RT-PCR at Day 10	**Number of Participants:** • IVM (n = 32) and SOC (n = 30) **Participant Characteristics:** • 71% of patients were male. • Mean age was 39.2 years (SD 12.1 years). • 81% of patients had mild disease and 19% had moderate disease. • Study provided no information on comorbidities. **Outcomes:** • Mean overall recovery time was 5.3 days (SD 2.5 days) in IVM arm and 6.3 days (SD 4.2 days) in SOC arm. The difference was not statistically significant. Time to resolution of fever, shortness of breath, and fatigue were no shorter in IVM arm. • Negative SARS-CoV-2 PCR result at Day 10: 18 of 20 patients (90%) in IVM arm, 19 of 20 (95%) in SOC arm.	**Key Limitations:** • Open-label study • Small study • Study enrolled young patients with mild disease who were unlikely to progress to severe COVID-19. **Interpretation:** • Compared to SOC, use of IVM did not lead to faster recovery from mild to moderate COVID-19. • The small sample size and large number of comparisons make it difficult to assess the clinical efficacy of IVM in this population.

Study Design	Methods	Results	Limitations and Interpretation
Ivermectin Plus Doxycycline Versus Hydroxychloroquine Plus Azithromycin for Asymptomatic Patients and Patients With Mild to Moderate COVID-19[23]			
RCT of outpatients with SARS-CoV-2 infection with or without symptoms in Bangladesh (n = 116)	**Key Inclusion Criteria:** • Laboratory-confirmed SARS-CoV-2 infection by RT-PCR • SpO_2 ≥95% • Normal or near-normal CXR • No unstable comorbidities **Interventions** *Group A:* • A single dose of IVM 200 µg/kg plus DOX 100 mg twice daily for 10 days *Group B:* • HCQ 400 mg on Day 1, then HCQ 200 mg twice daily for 9 days plus AZM 500 mg once daily for 5 days **Primary Endpoints:** • Time to negative PCR result. Asymptomatic patients were tested starting on Day 5, then every other day until a negative result occurred. Symptomatic patients were tested on their second symptom-free day, then every other day until a negative result occurred. • Time to resolution of symptoms	**Number of Participants:** • Group A (n = 60) and Group B (n = 56) **Participant Characteristics:** • Mean age was 33.9 years. • 78% of patients were male. • 91 of 116 patients (78.5%) were symptomatic. **Outcomes:** • PCR became negative in 60 of 60 patients (100%) in Group A and in 54 of 56 patients (96.4%) in Group B. • Mean time to negative PCR result: 8.93 days (range 8–13 days) in Group A, 9.33 days (range 5–15 days) in Group B (P = 0.2314). • Mean time to symptom recovery: 5.93 days (range 5–10 days) in Group A, 6.99 days (range 4–12 days) in Group B (P = 0.071). • In a subgroup analysis of patients who were symptomatic at baseline, the mean time to negative PCR result for Groups A and B were 9.06 days and 9.74 days, respectively (P = 0.0714). • Patients who received IVM plus DOX had fewer AEs than those who received HCQ plus AZM (31.7% vs. 46.4%) in the subgroup analysis.	**Key Limitations:** • Small sample size • Open-label study • No SOC alone group • Study enrolled young patients without major risk factors for disease progression. • None of the comparative outcome measures were statistically significant. **Interpretation:** • In this small study with a young population, the authors suggested that IVM plus DOX was superior to HCQ plus AZM despite no statistically significant difference in time from recovery to negative PCR result and symptom recovery between patients who received IVM plus DOX and those who received HCQ plus AZM.

Study Design	Methods	Results	Limitations and Interpretation
Antiviral Effect of High-Dose Ivermectin in Adults with COVID-19[24]			
Multicenter, randomized, open-label, blinded trial of hospitalized adults with mild to moderate COVID-19 in Argentina (n = 45)	**Key Inclusion Criteria:** • Laboratory-confirmed SARS-CoV-2 infection • Hospitalized • ≤5 days of symptoms **Key Exclusion Criteria:** • Use of immunomodulators or any agent with potential anti-SARS-CoV-2 activity prior to enrollment • Poorly controlled comorbidities **Interventions:** • IVM 600 µg/kg once daily plus SOC for 5 days • SOC **Primary Endpoint:** • VL reduction at Day 5. VL was quantified by NP swab at baseline, then at 24, 48, and 72 hours and Day 5. **PK Sampling:** • Performed 4 hours after dose on Days 1, 2, 3, 5, and 7 to assess elimination	**Number of Participants:** • IVM (n = 30) and SOC (n = 15) • After excluding patients with poor sample quality, those without a detectable VL at baseline, and those who withdrew, 32 patients (20 IVM, 12 SOC) were included in the viral efficacy analysis population. **Participant Characteristics:** • Mean age was 42.3±12.8 years in IVM arm and 38.1±11.7 years in SOC arm. • 50% of patients were male in IVM arm and 67% were male in SOC arm. **Primary Outcomes:** • By Day 5, a similar magnitude of VL reduction was seen in both arms. **Other Outcomes:** • Patients with higher IVM concentrations had greater reductions in VL (r 0.44; $P < 0.04$). • Treated patients were divided into 2 groups based on IVM C_{max}: IVM >160 ng/mL (median of 202 ng/mL) and <160 ng/mL (median of 109 ng/mL). • Median percentage of VL reduction by C_{max} concentration vs. control ($P = 0.0096$) was 72% (IQR 59% to 77%) in >160 ng/mL group (n = 9), 40% (IQR 21% to 46%) in <160 ng/mL group (n = 11), and 42% (IQR 31% to 73%) in SOC arm. • Median viral decay rate ($P = 0.04$) was 0.64 day^{-1} in >160 ng/mL group, 0.14 day^{-1} in <160 ng/mL group, and 0.13 day^{-1} in SOC arm. • Percentages of AEs were similar between the arms (43% in IVM arm, 33% in SOC arm), and AEs were mostly mild.	**Key Limitations:** • Small sample size • No clinical response data reported. • The C_{max} level of 160 ng/mL used in the analysis appears to be arbitrary. **Interpretation:** • Concentration-dependent virologic response was seen when using a higher-than-usual dose of IVM (600 µg/kg vs. 200 or 400 µg/kg once daily), with minimal associated toxicities. • The study results showed large interpatient variation of IVM C_{max}. Larger sample sizes are needed to further assess the safety and efficacy of using higher doses of IVM to treat COVID-19.

Study Design	Methods	Results	Limitations and Interpretation
Effect of Early Treatment With Ivermectin Versus Placebo on Viral Load, Symptoms, and Humoral Response in Patients With Mild COVID-19[25]			
A single-center, randomized, double-blind, placebo-controlled pilot trial in Spain (n = 24)	**Key Inclusion Criteria:** • Laboratory-confirmed SARS-CoV-2 infection • ≤72 hours of symptoms • No risk factors for severe disease or COVID-19 pneumonia **Interventions:** • Single dose of IVM 400 µg/kg • Nonmatching placebo tablet administered by a nurse who did not participate in the patient's care **Primary Endpoint:** • Positive SARS-CoV-2 PCR result from an NP swab at Day 7 post-treatment	**Number of Participants:** • IVM (n = 12) and placebo (n = 12) **Participant Characteristics:** • Mean age was 26 years (range 18–54 years). • 50% of patients were male. • All patients had symptoms at baseline; 70% had headache, 66% had fever, 58% had malaise, and 25% had cough. • Median onset of symptoms was 24 hours in IVM arm and 48 hours in placebo arm. **Outcomes:** • At Day 7, 12 patients (100%) in both groups had a positive PCR (for gene N), and 11 of 12 who received IVM (92%) and 12 of 12 who received placebo (100%) had a positive PCR (for gene E); *P* = 1.0 for both comparisons. • In a post hoc analysis, the authors reported fewer patient-days of cough and anosmia in the IVM-treated patients, but no differences in the patient-days for fever, general malaise, headache, and nasal congestion.	**Key Limitations:** • Small sample size • PCR is not a validated surrogate marker for clinical efficacy. • PCR cycle threshold values were higher for patients who received IVM than those who received placebo at some time points, but these comparisons are not statistically significant. • Symptom results were not a prespecified outcome and are of unclear statistical and clinical significance. **Interpretation:** • Patients who received IVM showed no difference in viral clearance compared to those who received placebo. • The small sample size and large number of comparisons make it difficult to assess the clinical efficacy of IVM in this population.

Study Design	Methods	Results	Limitations and Interpretation
Ivermectin Plus Doxycycline Plus Standard Therapy Versus Standard Therapy Alone in Patients With Mild to Moderate COVID-19[26]			
Randomized, unblinded, single-center study of patients with laboratory-confirmed SARS-CoV-2 infection in Baghdad, Iraq (n = 140) *This is a preliminary report that has not yet been peer reviewed.*	**Key Inclusion Criteria:** • Diagnosis by clinical, radiological, and PCR testing • Outpatients had mild or moderate COVID-19, while inpatients had severe and critical COVID-19. **Interventions:** • IVM 200 μg/kg PO daily for 2 days. If patient required more time to recover, a third dose was given 7 days after the first dose, plus DOX 100 mg twice daily for 5–10 days plus standard therapy (based on clinical condition). • Standard therapy was based on clinical condition and included AZM, acetaminophen, vitamin C, zinc, vitamin D3, dexamethasone 6 mg daily or methylprednisolone 40 mg twice daily if needed, and oxygen or mechanical ventilation if needed. • All critically ill patients were assigned to receive IVM plus DOX.	**Number of Participants:** • IVM plus DOX plus standard therapy (n = 70) and standard therapy alone (n = 70) **Participant Characteristics:** • Median age was 50 years in IVM arm and 47 years in standard therapy arm. • 50% of patients were male in IVM arm and 53% were male in standard therapy arm. • In IVM arm, 48 patients had mild or moderate COVID-19, 11 had severe COVID-19, and 11 had critical COVID-19. • In standard therapy arm, 48 patients had mild or moderate COVID-19, 22 had severe COVID-19, and no patients had critical COVID-19. **Outcomes:** • Mean recovery time in IVM arm was 10.1 days (SD 5.3 days) vs. 17.9 days (SD 6.8 days) for standard therapy arm ($P < 0.0001$). This result was only significant for those with mild to moderate disease. • Disease progression occurred in 3 of 70 patients (4.3%) in IVM arm and 7 of 70 (10.0%) in standard therapy arm ($P = 0.19$) • 2 of 70 patients (2.85%) in IVM arm and 6 of 70 (8.57%) in standard therapy arm died ($P = 0.14$)	**Key Limitations:** • Not blinded • Patient deaths prevent an accurate comparison of mean recovery time between arms in this study, and the authors did not account for competing mortality risks. • Relies heavily on post hoc subgroup comparisons. • Substantial imbalance in disease severity at baseline • Authors noted that critical patients were not assigned to standard therapy arm; thus, the arms were not truly randomized. • Unclear how many patients required corticosteroids. **Interpretation:** • IVM may shorten the time to recovery for patients with mild or moderate disease, but the lack of control for competing mortality causes in the study limits the ability to interpret the results.

Study Design	Methods	Results	Limitations and Interpretation
Ivermectin in Patients With Mild to Moderate COVID-19[27]			
Double-blind RCT in patients with mild to moderate COVID-19 in India (n = 157)	**Key Inclusion Criteria:** • Aged ≥18 years • Positive SARS-CoV-2 RT-PCR or antigen test • Nonsevere COVID-19 (defined as SpO_2 >90% on RA and no hypotension or need for mechanical ventilation) **Key Exclusion Criteria:** • CrCl <30 mL/min • Transaminases >5 times ULN • MI or heart failure in previous 90 days • QTc interval >450 ms • Severe comorbidity **Interventions:** • Single dose of IVM 24 mg in alcohol-based elixir prepared by pharmacy • Single dose of same elixir with IVM 12 mg • Single dose of same elixir without IVM (placebo) **Primary Endpoint:** • Reduction of SARS-CoV-2 VL as measured by NP and OP swab at Day 5 • Conversion to negative RT-PCR at Day 5 **Key Secondary Endpoints:** • Qualitative and quantitative RT-PCR on Days 3 and 7 • Time to clinical resolution	**Number of Participants:** • ITT analysis (safety): IVM 24 mg (n = 51), IVM 12 mg (n = 49), and placebo (n = 52) • mITT analysis (included only those with positive NP/OP RT-PCR result): IVM 24 mg (n = 40), IVM 12 mg (n = 40), and placebo (n = 45) • 64% of patients had mild disease (including asymptomatic disease) and 36% had moderate disease **Participant Characteristics:** • Mean age was 35.5 years (SD 10.4 years). • 88.8% of patients were male. • Mean BMI was 25. • Median duration of symptoms was similar between the arms (5 days; IQR 3–7 days). • 10% of patients received concurrent antivirals (RDV, favipiravir, or HCQ). No difference in use of antivirals between arms. **Primary Outcomes:** • Proportion of patients with negative RT-PCR result on Day 5: 47.5% in IVM 24 mg arm, 35.0% in IVM 12 mg arm, and 31.1% in placebo arm ($P = 0.30$) • VL at enrollment did not impact conversion to negative RT-PCR on Day 5. • No significant difference in VL decline by Day 5 between the arms • No difference in VL decline in the mild or moderate disease strata at Day 5 **Secondary Outcomes:** • No difference between arms in mean time to symptom resolution or number of hospital-free days at Day 28 • Proportions of patients with clinical worsening were similar across the arms: 7.5% in IVM 24 mg arm, 5.0% in IVM 12 mg arm, and 11.1% in placebo arm ($P = 0.65$)	**Key Limitations:** • Small sample size **Interpretation:** • Though the rate of negative RT-PCR results was numerically higher in the IVM arms than in the placebo arm on Day 5, the result was not statistically significant. • No difference in clinical outcomes or frequency of AEs.

Study Design	Methods	Results	Limitations and Interpretation
Ivermectin in Patients With Mild to Moderate COVID-19[27], continued			
	• Frequency of clinical worsening • Clinical status at Day 14 • Number of hospital-free days at Day 28	• No difference between arms in frequency of AEs or SAEs	
Efficacy and Safety of Ivermectin and Hydroxychloroquine in Patients With Severe COVID-19[28]			
Randomized, double-blind trial of hospitalized adults with COVID-19 pneumonia in Mexico (n = 106) *This is a preliminary report that has not yet been peer reviewed.*	**Key Inclusion Criteria:** • Laboratory-confirmed SARS-CoV-2 infection • Pneumonia, diagnosed by CXR or high-resolution chest CT scan • Recently established hypoxemic respiratory failure or deterioration of pre-existing lung or heart disease **Key Exclusion Criteria:** • Receipt of HFNC oxygen or invasive mechanical ventilation • Patients with QT intervals ≥500 ms were not eligible for HCQ but were eligible for IVM. **Interventions:** • HCQ 400 mg twice daily on Day 1, then HCQ 200 mg/kg twice daily for 4 days • Single dose of IVM 12 mg (in patients weighing ≤80 kg) or 18 mg (in those weighing >80 kg) plus calcium citrate for subsequent doses • Calcium citrate placebo **Primary Endpoint:** • Time to discharge due to recovery	**Number of Participants:** • HCQ (n = 33), IVM (n = 36), and placebo (n = 37) **Participant Characteristics:** • Mean age was 53 years (SD 16.9 years). • 62% of patients were male. • 34% of patients had diabetes, 32% had hypertension, and 72% had any comorbidity. • Mean BMI was 29.6 (SD 6.6). **Outcomes:** • Median time to discharge due to recovery was 7 days (IQR 3–9 days) in HCQ arm, 6 days (IQR 4–11 days) in IVM arm, and 5 days (IQR 4–7 days) in placebo arm. The differences between arms were not statistically significant. • Proportion of patients discharged alive: 79% in HCQ arm, 75% in IVM arm, and 73% in placebo arm • Mortality: 6% of patients in HCQ arm, 14% in IVM arm, and 16% in placebo arm	**Key Limitations:** • Small study • Length of follow-up period is unclear. • The study was stopped prior to achieving its target sample size. **Interpretation:** • In hospitalized patients with COVID-19 pneumonia who were not critically ill, neither IVM nor HCQ decreased the number of in-hospital days, rate of respiratory deterioration, or mortality. • The small sample size and large number of comparisons make it difficult to assess the clinical efficacy of IVM in this population.

Study Design	Methods	Results	Limitations and Interpretation
Ivermectin as Adjunctive Therapy to Hospitalized Patients With COVID-19[29]			
Randomized, double-blind, placebo-controlled, multicenter, Phase 2 clinical trial of hospitalized adults with mild to severe SARS-CoV-2 infection in 5 facilities in Iran (n = 180) *This is a preliminary report that has not yet been peer reviewed.*	**Key Inclusion Criteria:** • Symptoms suggestive of COVID-19 pneumonia, with chest CT compatible with mild to severe COVID-19 or positive RT-PCR result for SARS-CoV-2 **Key Exclusion Criteria:** • Severe immunosuppression, malignancy, or chronic kidney disease • Pregnancy **Interventions:** • HCQ 200 mg/kg twice daily alone as SOC (standard arm) • SOC plus 1 of the following: • Placebo • Single dose of IVM 200 µg/kg • IVM 200 µg/kg on Days 1, 3, and 5 • Single dose of IVM 400 µg/kg • IVM 400 µg/kg on Day 1, then IVM 200 µg/kg on Days 3 and 5 **Primary Endpoint:** • Clinical recovery within 45 days of enrollment (defined as normal temperature, respiratory rate, and SpO_2 >94% for 24 hours)	**Number of Participants:** • All 6 arms (n = 30 in each arm) **Participant Characteristics:** • Average age was 56 years (range 45–67 years). • 50% of patients were male. • Disease stratification (based on CT findings): negative (1%), mild (14%), moderate (73%), and severe (12%) • Mean SpO_2 at baseline was 89%. **Primary Outcomes:** • Durations of hypoxemia and hospitalization were shorter in IVM arms than placebo arm ($P = 0.025$ and $P = 0.006$, respectively), and mortality was lower in the IVM arms ($P = 0.001$). • There was no difference in number of days of tachypnea ($P = 0.584$) or return to normal temperature ($P = 0.102$). • Significant differences in change from baseline to Day 5 in absolute lymphocyte count, platelet count, erythrocyte sedimentation rate, and CRP. • Higher mortality was reported in standard and placebo arms than IVM arms.	**Key Limitations:** • Small study • Power estimation is confusing. • Mortality was not listed as the primary or secondary outcome. • It is unclear whether IVM patients also received HCQ. • It is unclear whether the between-group comparisons are between combined IVM groups and placebo plus SOC. • Patients were stratified by disease severity based on CT findings. These categorizations are unclear and were not taken into account in outcome comparisons. • The post hoc grouping of randomized arms raises risk of false positive findings. **Interpretation:** • IVM appeared to improve laboratory outcomes and some clinical outcomes (shorter duration of hypoxemia and hospitalization) and lowered mortality. • The small size of the study, the unclear treatment arm assignments, and the lack of accounting for disease severity at baseline make it difficult to draw conclusions about the efficacy of using IVM to treat patients with mild COVID-19.

Study Design	Methods	Results	Limitations and Interpretation
Retrospective Analysis of Ivermectin in Hospitalized Patients With COVID-19[30]			
Retrospective analysis of consecutive patients with laboratory-confirmed SARS-CoV-2 infection who were admitted to 4 Florida hospitals (n = 276)	**Key Inclusion Criteria:** • Positive NP swab with SARS-CoV-2 RNA **Interventions:** • Single dose of IVM 200 μg/kg, repeated on Day 7 at the doctors' discretion; 90% of patients also received HCQ. • Usual care: 97% of patients received HCQ and most also received AZM. **Primary Endpoint:** • All-cause, in-hospital mortality	**Number of Participants:** • IVM (n = 173; 160 patients received a single dose, 13 patients received a second dose) and usual care (n = 103) **Participant Characteristics:** • Mean age was 60.2 years in IVM arm and 58.6 years in usual care arm. • 51.4% of patients were male in IVM arm and 58.8% were male in usual care arm. • 56.6% of patients were Black in IVM arm and 51.4% were Black in usual care arm. **Outcomes:** • All-cause mortality was lower in IVM arm than in usual care arm (OR 0.27; 95% CI, 0.09–0.80; $P = 0.03$); the benefit appeared to be limited to the subgroup of patients with severe disease. • No difference in median length of hospital stay between arms (7 days for both) or proportion of mechanically ventilated patients who were successfully extubated (36% in IVM arm vs. 15% in usual care arm; $P = 0.07$).	**Key Limitations:** • Not randomized • Little to no information on SpO_2 or radiographic findings • Timing of therapeutic interventions was not standardized. • Ventilation and hospitalization duration analyses do not appear to account for death as a competing risk. • No virologic assessments were performed. **Interpretation:** • IVM use was associated with lower mortality than usual care. However, the limitations of this retrospective analysis make it difficult to draw conclusions about the efficacy of using IVM to treat patients with COVID-19.

Study Design	Methods	Results	Limitations and Interpretation
Observational Study on the Effectiveness of Hydroxychloroquine, Azithromycin, and Ivermectin Among Hospitalized Patients With COVID-19[31]			
Retrospective cohort study of hospitalized adults with COVID-19 in Peru (n = 5,683) *This is a preliminary report that has not yet been peer-reviewed.*	**Key Inclusion Criteria:** • Aged ≥18 years • Symptomatic • Laboratory-confirmed SARS-CoV-2 infection • No life-threatening illness at admission **Key Exclusion Criteria:** • Required oxygen at admission • Use of tocilizumab, LPV/RTV, or RDV **Interventions:** • One of the following interventions administered within 48 hours of admission: • HCQ or CQ alone • IVM alone • AZM alone • HCQ or CQ plus AZM • IVM plus AZM • SOC (e.g., supportive care, antipyretics, hydration) **Primary Endpoint:** • All-cause mortality **Secondary Endpoint:** • All-cause mortality and/or transfer to ICU	**Number of Participants:** • HCQ or CQ alone (n = 200), IVM alone (n = 203), AZM alone (n = 1,600), HCQ or CQ plus AZM (n = 692), IVM plus AZM (n = 358), and SOC (n = 2,630) **Participant Characteristics:** • 63% of patients were male. • Mean age was 59.4 years (range 18–104 years). • All patients had mild or moderate disease. **Outcomes:** • Median follow-up time was 7 days. Mortality rate was 18.9% at the end of follow-up. • IVM alone was associated with increased risk of death and/or ICU transfer compared to SOC (wHR 1.58; 95% CI, 1.11–2.25). • IVM plus AZM did not have an effect on deaths or any secondary outcomes (all-cause death and/or ICU transfer, all-cause death and/or oxygen prescription) compared to SOC. • HCQ or CQ plus AZM was associated with a higher risk of death (wHR 1.84; 95% CI, 1.12–3.02), death and/or ICU transfer (wHR 1.49; 95% CI, 1.01–2.19), and death and/or oxygen prescription (wHR 1.70; 95% CI, 1.07–2.69) compared to SOC.	**Key Limitations:** • Not randomized • Unclear whether all patients received IVM or other medications according to Peruvian guidelines referred to in the manuscript. • Dosing and timing of administration are unclear. **Interpretation:** • Compared to SOC, IVM alone was associated with increased risk of death and/or ICU admission. Using IVM in combination with AZM was not associated with effects on mortality, ICU transfer, or oxygen prescription compared to SOC.

Study Design	Methods	Results	Limitations and Interpretation
Retrospective Study of Ivermectin Versus Standard of Care in Patients With COVID-19[32]			
Retrospective study of consecutive adult patients hospitalized in Bangladesh with laboratory-confirmed SARS-CoV-2 infection (n = 248)	**Key Inclusion Criteria:** • Aged ≥18 years • Positive NP swab with SARS-CoV-2 RNA • "Free from any other serious pathological conditions" **Interventions:** • Single dose of IVM 12 mg within 24 hours of hospital admission • SOC **Primary Outcome:** • Not specified	**Number of Participants:** • IVM (n = 115) and SOC (n = 133) **Participant Characteristics:** • Median age in IVM arm was 34 years; 70% of patients were male. • Median age in SOC arm was 35 years; 52% of patients were male. • All patients had mild or moderate disease. • 12% of patients had hypertension in both arms. • 17% of patients in IVM arm and 12% in SOC arm had DM. **Outcomes:** • Fewer patients in IVM arm had evidence of disease progression compared to SOC arm ($P < 0.001$): moderate respiratory distress (2.6% vs. 15.8%), pneumonia (0% vs. 9.8%), ischemic stroke (0% vs. 1.5%). • Fewer patients in IVM arm required intensive care management compared to SOC arm (0.9% vs. 8.8%; $P < 0.001$). • Fewer patients in IVM arm required antibiotic therapy (15.7% vs. 60.2%; $P < 0.001$) or supplemental oxygen (9.6% vs. 45.9%; $P < 0.001$) compared to SOC arm. • Shorter median duration of viral clearance in IVM arm compared to SOC arm (4 vs. 15 days; $P < 0.001$). • Shorter median duration of hospital stay in IVM arm compared to SOC arm (9 vs. 15 days; $P < 0.001$) • Lower mortality in IVM arm compared to SOC arm (0.9% vs. 6.8%; $P < 0.05$)	**Key Limitations:** • Not randomized • Disease severity at admission was reported as mild or moderate, but 12% of patients in IVM arm and 9% in SOC arm had SpO_2 <94% • Even though only 10% of patients developed pneumonia, 60% received antibiotics. • Possibility of harm from concomitant medications **Interpretation:** • Compared to SOC, IVM use was associated with faster rates of viral clearance and better clinical outcomes, including shorter hospital stay and lower mortality.

Key: AE = adverse event; AZM = azithromycin; BMI = body mass index; CAD = coronary artery disease; C_{max} = maximum concentration; CQ = chloroquine; CrCl = creatinine clearance; CRP = C-reactive protein; CT = computed tomography; CXR = chest X-ray; CYP = cytochrome P450; DM = diabetes mellitus; DOX = doxycycline; HCQ = hydroxychloroquine; HFNC = high-flow nasal cannula; HTN = hypertension; ICU = intensive care unit; Ig = immunoglobulin; ITT = intention-to-treat; IVM = ivermectin; LDH = lactose dehydrogenase; LPV/RTV = lopinavir/ritonavir; MDR1 = multidrug resistance mutation 1; MI = myocardial infarction; mITT = modified intention-to-treat; NP = nasopharyngeal; OP = oropharyngeal; 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; PK = pharmacokinetic; PO = orally; r = correlation coefficient; RA = room air; RCT = randomized controlled trial; RDV = remdesivir; RT-PCR = reverse transcriptase polymerase chain reaction; SAE = severe adverse event; SNP = single-nucleotide polymorphism; SOC = standard of care; SOFA = sequential organ failure assessment; SpO_2 = oxygen saturation; ULN = upper limit of normal; VL = viral load

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Lopinavir/Ritonavir and Other HIV Protease Inhibitors

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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]

- In a large international randomized trial, lopinavir/ritonavir did not reduce the mortality rate among hospitalized patients with COVID-19.[5]
- A moderately sized randomized trial (n = 199) failed to find a virologic or clinical benefit of lopinavir/ritonavir over standard of care.[6]
- Results from a small randomized controlled trial showed that darunavir/cobicistat was not effective for the treatment of COVID-19.[7]
- There are no data from clinical trials that support using other HIV protease inhibitors to treat COVID-19.
- Please see Clinical Data for COVID-19 below for more information.

Clinical Data for COVID-19

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

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

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

Patients were randomized into several parallel treatment arms; this included randomization in a 2:1 ratio to receive either the usual standard of care only or the usual standard of care plus lopinavir 400 mg/ritonavir 100 mg orally every 12 hours for 10 days or until hospital discharge. Patients who had severe hepatic insufficiency or who were receiving medications that had potentially serious or life-threatening interactions with lopinavir/ritonavir were excluded from randomization into either of these arms. Mechanically ventilated patients were also underrepresented in this study because it was difficult to administer the oral tablet formulation of lopinavir/ritonavir to patients who were on mechanical ventilation. The primary outcome was all-cause mortality at Day 28 after randomization.

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

Patient Characteristics

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

period were similar in both arms (23% in the lopinavir/ritonavir arm vs. 25% in the standard of care arm). In addition, 10% of patients in both arms received dexamethasone.

Results

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

Limitations

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

Interpretation

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

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

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

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

Patient Characteristics

- In both the lopinavir/ritonavir arm and the standard of care arm, 20% of the participants were aged ≥70 years and 37% were aged <50 years.
- Comorbidities were common. Diabetes mellitus was present in 24% of patients, heart disease in 21%, and chronic lung disease in 7%.

- At randomization, 8% of patients were receiving invasive mechanical ventilation or extracorporeal membrane oxygenation, 53% were receiving oxygen only (with or without noninvasive ventilation), and 39% were receiving neither.
- Similar percentages of patients received corticosteroids in the lopinavir/ritonavir arm and the standard of care arm (23% vs. 24%). Other nonstudy treatments were administered less often, and the use of these treatments was balanced between arms.

Results

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

Limitations

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

Interpretation

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

Lopinavir/Ritonavir Pharmacokinetics in Patients With COVID-19

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

Results

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

Limitations

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

Interpretation

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

Other Reviewed Studies

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

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Nitazoxanide

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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 2d 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 2e 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 women.

Considerations in Children

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

Clinical Trials

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

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Table 2d. Nitazoxanide: Selected Clinical Data

Last Updated: July 8, 2021

The information in this table may include data from preprints or articles that have not been peer reviewed. This section will be updated as new information becomes available. Please see 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.

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.

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

Last Updated: July 8, 2021

- The information in this table is derived from data on the use of these drugs for FDA-approved indications or in investigational trials, and it is supplemented with data on their use in patients with COVID-19, when available.
- Information on CQ, HCQ, and LPV/RTV are available in the archived versions of the Guidelines. However, the Panel **recommends against** using these agents to treat COVID-19.
- There are limited or no data on dose modifications for patients with organ failure or those who require extracorporeal devices. Please refer to product labels, when available.
- There are currently not enough data to determine whether certain medications can be safely coadministered with therapies for the treatment of COVID-19. When using concomitant medications with similar toxicity profiles, consider performing additional safety monitoring.
- The potential additive, antagonistic, or synergistic effects and the safety of using combination therapies for the treatment of COVID-19 are unknown. Clinicians are encouraged to report AEs to the FDA *MedWatch* program.
- For drug interaction information, please refer to product labels and visit the Liverpool COVID-19 Drug Interactions website.
- For the Panel's recommendations on using the drugs listed in this table, please refer to the individual drug sections or Therapeutic Management of Hospitalized Adults With COVID-19.

Dosing Regimens *The doses listed here are for approved indications or from reported experiences or clinical trials.*	**Adverse Events**	**Monitoring Parameters**	**Drug-Drug Interaction Potential**	**Comments and Links to Clinical Trials**
Remdesivir				
The doses and indications listed below come from the FDA product information. Please see Therapeutic Management of Hospitalized Adults With COVID-19 for the Panel's recommendations on when to use RDV. **For Hospitalized Adults and Children (Aged ≥12 Years and Weighing ≥40 kg)**	• 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.	• Infusion reactions • Renal function and hepatic function should be monitored before and during treatment as clinically indicated. • In the FDA product information, RDV **is not recommended** when eGFR is <30 mL/min. See the Remdesivir section for a discussion on using RDV in people with renal insufficiency.	• Clinical drug-drug interaction studies of RDV have not been conducted. • In vitro, RDV is a substrate of CYP3A4, OATP1B1, and P-gp and an inhibitor of CYP3A4, OATP1B1, OATP1B3, and MATE1.[1]	• RDV should be administered in a hospital or a health care setting that can provide a similar level of care to an inpatient hospital. • RDV is approved by the FDA for the treatment of COVID-19 in hospitalized adult and pediatric patients (aged ≥12 years and weighing ≥40 kg).

Dosing Regimens *The doses listed here are for approved indications or from reported experiences or clinical trials.*	**Adverse Events**	**Monitoring Parameters**	**Drug-Drug Interaction Potential**	**Comments and Links to Clinical Trials**
Remdesivir, continued				
For Patients Who Are Not Mechanically Ventilated and/or on ECMO: • RDV 200 mg IV[a] on Day 1, then RDV 100 mg IV on Days 2–5 • For patients who do not show clinical improvement after 5 days of therapy, treatment may be extended to up to 10 days. *For Mechanically Ventilated Patients and/or Patients on ECMO:* • RDV 200 mg IV[a] on Day 1, then RDV 100 mg IV on Days 2–10 **Suggested Dose in EUA[b] for Hospitalized Children** *For Patients Weighing 3.5 kg to <40 kg:* • RDV 5 mg/kg IV[a] on Day 1, then RDV 2.5 mg/kg IV once daily starting on Day 2 • For patients who are not mechanically ventilated and/or on ECMO, the duration is 5 days. If patients have not shown clinical improvement after 5 days, treatment may be extended to up to 10 days. • For mechanically ventilated patients and/or patients on ECMO, the recommended treatment duration is 10 days. *For Patients Aged <12 Years and Weighing ≥40 kg:* • Same dose as for adults	• 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.	• RDV may need to be discontinued if ALT level increases to >10 times ULN and should be discontinued if there is an increase in ALT level and signs or symptoms of liver inflammation are observed.[1]	• Minimal to no reduction in RDV exposure is expected when RDV is coadministered with dexamethasone (Gilead Sciences, written communication, July 2020). • CQ or HCQ may decrease the antiviral activity of RDV; coadministration of these drugs **is not recommended**.[1] • No significant interaction is expected between RDV and oseltamivir or baloxavir (Gilead Sciences, personal and written communications, August and September 2020).	• An EUA[b] is available for hospitalized pediatric patients weighing 3.5 kg to <40 kg or aged <12 years and weighing ≥3.5 kg. • A list of clinical trials is available here: Remdesivir

Dosing Regimens *The doses listed here are for approved indications or from reported experiences or clinical trials.*	**Adverse Events**	**Monitoring Parameters**	**Drug-Drug Interaction Potential**	**Comments and Links to Clinical Trials**
Ivermectin				
Adults: • The dose most commonly used in clinical trials is IVM 0.2–0.6 mg/kg PO given as a single dose or as a once-daily dose for up to 5 days.	• Generally well tolerated • Dizziness • Pruritis • GI effects (e.g., nausea, diarrhea) • Neurological AEs have been reported 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.[2] • A list of clinical trials is available here: Ivermectin
Nitazoxanide				
Adults: • Doses reported in COVID-19 studies range from NTZ 500 mg PO 3 times daily to 4 times daily.[3,4] Higher doses are being studied (ClinicalTrials.gov Identifier NCT04746183). • Doses used for antiprotozoal indications range from NTZ 500 mg to 1 g PO twice daily.	• Generally well tolerated • 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 here: Nitazoxanide

[a] Infuse over 30–120 minutes.

[b] The FDA EUA permits the emergency use of RDV for the treatment of suspected COVID-19 or laboratory-confirmed SARS-CoV-2 infection in hospitalized pediatric patients weighing 3.5 kg to <40 kg or aged <12 years and weighing ≥3.5 kg.[6]

Key: AE = adverse event; ALT = alanine transaminase; AST = aspartate aminotransferase; CQ = chloroquine; CYP = cytochrome P450; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; GI = gastrointestinal; HCQ = hydroxychloroquine; IV = intravenous; IVM = ivermectin; LPV/RTV = lopinavir/ritonavir; MATE = multidrug and toxin extrusion protein; NTZ = nitazoxanide; OATP = organic anion transporter polypeptide; the Panel = the COVID-19 Treatment Guidelines Panel; P-gp = P-glycoprotein; PO = orally; RDV = remdesivir; SBECD = sulfobutylether-beta-cyclodextrin; ULN = upper limit of normal

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Anti-SARS-CoV-2 Antibody Products

Last Updated: October 19, 2021

Summary Recommendations
Anti-SARS-CoV-2 Monoclonal Antibodies for the Treatment of COVID-19 • The COVID-19 Treatment Guidelines Panel (the Panel) recommends using one of the following anti-SARS-CoV-2 monoclonal antibody (mAb) products (listed alphabetically and not in order of preference) to treat nonhospitalized patients with mild to moderate COVID-19 who are at high risk of clinical progression, as defined by criteria in the Food and Drug Administration (FDA) Emergency Use Authorizations (EUAs) for the products: • **Bamlanivimab 700 mg plus etesevimab 1,400 mg** administered as an intravenous (IV) infusion in regions where the combined frequency of potentially resistant SARS-CoV-2 variants is low (see the FDA webpage Bamlanivimab and Etesevimab Authorized States, Territories, and U.S. Jurisdictions); *or*   • **Casirivimab 600 mg plus imdevimab 600 mg** administered as an IV infusion or as subcutaneous (SQ) injections; *or*   • **Sotrovimab 500 mg** administered as an IV infusion • When using casirivimab plus imdevimab, the Panel recommends: • **Casirivimab 600 mg plus imdevimab 600 mg** administered as an IV infusion **(AIIa)**   • If an IV infusion is not feasible or would cause a delay in treatment, **casirivimab 600 mg plus imdevimab 600 mg** can be administered as four SQ injections (2.5 mL per injection) **(BIII)**. • 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 risk for progression to severe COVID-19 and/or hospitalization (see Anti-SARS-CoV-2 Monoclonal Antibodies). The ratings for the recommendations for using anti-SARS-CoV-2 mAbs as treatment are based on the FDA EUA criteria for: • High-risk conditions that were represented in patients in clinical trials **(AIIa)**, *and*   • Other medical conditions and factors that had limited representation in patients in clinical trials **(BIII)**; however, for immunocompromising conditions or receipt of immunosuppressive therapy, the rating is **AIII**. • When using anti-SARS-CoV-2 mAbs, treatment should be started as soon as possible after the patient receives a positive result on a SARS-CoV-2 antigen test or nucleic acid amplification test (NAAT) and within 10 days of symptom onset. • The availability of bamlanivimab plus etesevimab was previously restricted in areas with an elevated combined frequency of variants that have markedly reduced in vitro susceptibility to these agents (e.g., the Gamma and Beta variants). See the FDA webpage Bamlanivimab and Etesevimab Authorized States, Territories, and U.S. Jurisdictions for updates on the distribution of bamlanivimab plus etesevimab. • The use of 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 EUA criteria for outpatient treatment. • Anti-SARS-CoV-2 mAbs are not currently authorized for use in patients who are hospitalized with severe COVID-19; however, they may be available through expanded access programs for patients who either have not developed an antibody response or are not expected to mount an effective immune response to SARS-CoV-2 infection. **Anti-SARS-CoV-2 Monoclonal Antibodies as Post-Exposure Prophylaxis for SARS-CoV-2 Infection** • The Panel recommends using one of the following anti-SARS-CoV-2 mAb combinations as post-exposure prophylaxis (PEP) for people who are at high risk for progression to severe COVID-19 if infected with SARS-CoV-2 **AND** who have the vaccination status **AND** exposure history as outlined in the Prevention of SARS-CoV-2 Infection section: • **Bamlanivimab 700 mg plus etesevimab 1,400 mg** administered as an IV infusion; *or*   • **Casirivimab 600 mg plus imdevimab 600 mg** administered as SQ injections **(AI)** or as an IV infusion **(BIII)**. **COVID-19 Convalescent Plasma** • The Panel **recommends against** the use of **low-titer COVID-19 convalescent plasma** for the treatment of COVID-19 **(AIIb)**. Low-titer COVID-19 convalescent plasma is no longer authorized through the convalescent plasma EUA.

Summary Recommendations, continued
• For hospitalized patients with COVID-19 who do not have impaired immunity: • The Panel **recommends against** the use of **COVID-19 convalescent plasma** for the treatment of COVID-19 in mechanically ventilated patients **(AI)**. • The Panel **recommends against** the use of **high-titer COVID-19 convalescent plasma** for the treatment of COVID-19 in hospitalized patients who do not require mechanical ventilation, except in a clinical trial **(AI).** • For hospitalized patients with COVID-19 who have impaired immunity: • There is insufficient evidence for the Panel to recommend either for or against the use of high-titer COVID-19 convalescent plasma for the treatment of COVID-19. • For nonhospitalized patients with COVID-19: • There is insufficient evidence for the Panel to recommend either for or against the use of high-titer COVID-19 convalescent plasma for the treatment of 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 = Optional **Rating of Evidence:** I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

Anti-SARS-CoV-2 Monoclonal Antibodies

Last Updated: October 19, 2021

The SARS-CoV-2 genome encodes four 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 two subunits, S1 and S2, that mediate host cell attachment and invasion. Through its receptor-binding domain (RBD), S1 attaches to angiotensin-converting enzyme 2 (ACE2) on the host cell; this initiates a conformational change in S2 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 a clinical benefit in treating SARS-CoV-2 infection (as discussed below). Some anti-SARS-CoV-2 mAbs have been found to be effective in preventing SARS-CoV-2 infection in household contacts of infected patients[2] and during SARS-CoV-2 outbreaks in skilled nursing and assisted living facilities.[3]

Anti-SARS-CoV-2 Monoclonal Antibodies That Have Received Emergency Use Authorizations From the Food and Drug Administration

Currently, three anti-SARS-CoV-2 mAb products have received Emergency Use Authorizations (EUAs) from the Food and Drug Administration (FDA) 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 and/or hospitalization. The issuance of an EUA does not constitute FDA approval. These products are:

- *Bamlanivimab plus etesevimab:* These are neutralizing mAbs that bind to different, but overlapping, epitopes in the spike protein RBD of SARS-CoV-2.
  - The distribution of bamlanivimab plus etesevimab was paused in the United States because both the Gamma (P.1) and Beta (B.1.351) variants have reduced susceptibility to bamlanivimab and etesevimab.[4] However, distribution of the agents has been reinstated in states with low rates of these and other variants that have reduced susceptibility to bamlanivimab and etesevimab. Please refer to the FDA webpage Bamlanivimab and Etesevimab Authorized States, Territories, and U.S. Jurisdictions for the latest information on bamlanivimab plus etesevimab distribution.
- *Casirivimab plus imdevimab:* These are recombinant human mAbs that bind to nonoverlapping epitopes of the spike protein RBD of SARS-CoV-2.
- *Sotrovimab:* This mAb was originally identified in 2003 from a SARS-CoV survivor. It targets an epitope in the RBD of the spike protein that is conserved between SARS-CoV and SARS-CoV-2.

The FDA has expanded the EUAs for bamlanivimab plus etesevimab and casirivimab plus imdevimab to authorize their use as post-exposure prophylaxis (PEP) for certain individuals who are at high risk of acquiring SARS-CoV-2 infection and, if infected, are at high risk of progressing to serious illness. See Prevention of SARS-CoV-2 Infection and the FDA EUA fact sheets for bamlanivimab plus etesevimab and casirivimab plus imdevimab for more information.

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

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. For recommendations and discussion regarding the use of mAb products as PEP, see Prevention of SARS-CoV-2 Infection.

Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using one of the following anti-SARS-CoV-2 mAb products (listed alphabetically and **not** in order of preference) to treat nonhospitalized patients with mild to moderate COVID-19 who are at high risk of clinical progression (see the EUA criteria for use of the products and the related discussion below):
  - **Bamlanivimab 700 mg plus etesevimab 1,400 mg** administered as an intravenous (IV) infusion in regions where the combined frequency of potentially resistant SARS-CoV-2 variants is low (see the FDA webpage Bamlanivimab and Etesevimab Authorized States, Territories, and U.S. Jurisdictions; *or*
  - **Casirivimab 600 mg plus imdevimab 600 mg** administered as an IV infusion or as subcutaneous (SQ) injections; *or*
  - **Sotrovimab 500 mg** administered as an IV infusion.
- When using casirivimab plus imdevimab, the Panel recommends:
  - **Casirivimab 600 mg plus imdevimab 600 mg** administered as an IV infusion **(AIIa)**
  - If an IV infusion is not feasible or would cause a delay in treatment, **casirivimab 600 mg plus imdevimab 600 mg** can be administered as four SQ injections (2.5 mL per injection) **(BIII)**.
- When using anti-SARS-CoV-2 mAbs, treatment should be started as soon as possible after the patient receives a positive result on a SARS-CoV-2 antigen test or nucleic acid amplification test (NAAT) and within 10 days of symptom onset.
- The use of 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 EUA criteria for outpatient treatment.
- Anti-SARS-CoV-2 mAbs are not currently authorized for use in patients who are hospitalized with severe COVID-19; however, they may be available through expanded access programs for patients who either have not developed an antibody response to SARS-CoV-2 infection or are not expected to mount an effective immune response to infection.
- For guidance on prioritizing the use of anti-SARS-CoV-2 mAbs for the treatment or prevention of SARS-CoV-2 infection when logistical or supply constraints limit their availability, see The Panel's Updated Statement on the Prioritization of Anti-SARS-CoV-2 Monoclonal Antibodies.

Rationale

In randomized, placebo-controlled trials in nonhospitalized patients who had 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).[5-7] It is worth noting that these studies were conducted before the widespread circulation of variants of concern (VOC). The potential impact of these variants and their susceptibility to different anti-SARS-CoV-2 mAbs is discussed below.

Bamlanivimab Plus Etesevimab

This anti-SARS-CoV-2 mAb combination has demonstrated a clinical benefit in people with mild to moderate COVID-19 who are at high risk for progression to severe disease and/or hospitalization (see Table 3a). The distribution of bamlanivimab plus etesevimab was paused in the United States because both the Gamma (P.1) and Beta (B.1.351) variants have reduced susceptibility to bamlanivimab and etesevimab.[4] However, distribution of the product has been reinstated across the United States because the combined frequency of the Gamma and Beta variants is <5%. Casirivimab plus imdevimab and sotrovimab are expected to remain active against the Gamma and Beta variants.

The FDA provides a list of states, territories, and U.S. jurisdictions in which bamlanivimab plus etesevimab is currently authorized. The Centers for Disease Control and Prevention (CDC) COVID-19 Data Tracker website has the latest information on variant frequencies by region in the United States.

Casirivimab Plus Imdevimab

On June 3, 2021, the FDA updated the EUA for casirivimab plus imdevimab to reduce the authorized dosage for a single IV infusion from casirivimab 1,200 mg plus imdevimab 1,200 mg to casirivimab 600 mg plus imdevimab 600 mg.[6] The update also authorized SQ injection of these lower doses of casirivimab and imdevimab if an IV infusion is not feasible or would delay treatment. SQ administration requires four injections (2.5 mL per injection) at four different sites (see the FDA EUA for details).

The recommendation for using the lower dose of casirivimab 600 mg plus imdevimab 600 mg IV is based on the Phase 3 results from the R10933-10987-COV-2067 study (ClinicalTrials.gov Identifier NCT04425629). This double-blind, placebo-controlled randomized trial in outpatients with mild to moderate COVID-19 evaluated different doses of casirivimab plus imdevimab. The modified full analysis set included participants aged ≥18 years who had a positive SARS-CoV-2 polymerase chain reaction result at randomization and who had one or more risk factors for progression to severe COVID-19. The results demonstrated a 2.2% absolute reduction and a 70% relative reduction in hospitalization or death with receipt of casirivimab 600 mg plus imdevimab 600 mg. These results are comparable to the those observed for IV infusions of casirivimab 1,200 mg plus imdevimab 1,200 mg, which demonstrated a 3.3% absolute reduction and a 71% relative reduction in hospitalization or death among patients who received this higher dose of casirivimab plus imdevimab.[8] See Table 3a for additional details from the trial.

The recommendation for using SQ injections to administer casirivimab plus imdevimab is based on safety data from the Phase 1 R10933-10987-HV-2093 study (ClinicalTrials.gov Identifier NCT04519437). This double-blind, placebo-controlled randomized trial compared casirivimab plus imdevimab administered by SQ injection to placebo in healthy volunteers who did not have SARS-CoV-2 infection. Injection site reactions were observed in 12% of the 729 casirivimab plus imdevimab recipients and in 4% of the 240 placebo recipients. According to the FDA EUA, in a separate trial that evaluated casirivimab plus imdevimab in symptomatic participants, there were similar reductions in viral load in the participants in the IV and SQ arms of the trial.[6] However, because the safety and efficacy data for **casirivimab plus imdevimab** administered by SQ injection are limited, this route of administration should only be used when IV infusion is not feasible or would lead to a delay in treatment **(BIII)**.

Sotrovimab

The data that support the EUA for sotrovimab are from the Phase 3 COMET-ICE trial (ClinicalTrials.gov Identifier NCT04545060). The COMET-ICE trial included outpatients with mild to moderate COVID-19 who were at high risk for progression to severe disease and/or hospitalization. A total of 583 participants were randomized to receive sotrovimab 500 mg IV (n = 291) or placebo (n = 292). 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 3 of 291 participants (1%) in the sotrovimab arm and 21 of 292 participants (7%) in the placebo arm ($P = 0.002$), resulting in a 6% absolute reduction and an 85% relative reduction in hospitalizations or death associated with sotrovimab.[7]

Criteria for Using Anti-SARS-CoV-2 Monoclonal Antibodies Under the Emergency Use Authorizations

The FDA EUAs for the 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.[5,6] 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 agents in patients with the following conditions: sickle cell disease, neurodevelopmental disorders, medical-related technological dependence, asthma, cardiovascular disease, hypertension, and chronic lung disease.

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 and/or hospitalization. The ratings for the recommendations for the use of anti-SARS-CoV-2 mAbs as treatment are based on the FDA EUA criteria for the following.

Medical Conditions or Other Factors That Were Represented in Patients in Clinical Trials That Evaluated Anti-SARS-CoV-2 Monoclonal Antibodies

- 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)**

Other Conditions or Factors That Had Limited Representation in Patients in Clinical Trials but Are Considered Risk Factors for Progression to Severe COVID-19 by the Centers for Disease Control and Prevention

- An immunocompromising condition or immunosuppressive treatment **(AIII)**. Many experts strongly recommend therapy for patients with these conditions, despite their limited representation in clinical trials.
- Being overweight (BMI 25–30) as the sole risk factor **(BIII)**
- Chronic kidney disease **(BIII)**
- Pregnancy **(BIII)**
- Sickle cell disease **(BIII)**
- Neurodevelopmental disorders (e.g., cerebral palsy) or other conditions that confer medical complexity (e.g., genetic or metabolic syndromes and severe congenital anomalies) **(BIII)**
- Medical-related technological dependence (e.g., tracheostomy, gastrostomy, or positive pressure ventilation that is not related to COVID-19) **(BIII)**

It is important to note that the likelihood of developing severe COVID-19 increases when a person has multiple high-risk conditions or comorbidities.[9-12] Medical conditions or other factors (e.g., race or ethnicity) not listed in the 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 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.[7]

Some of the Panel's recommendations for using anti-SARS-CoV-2 mAbs according to the updated EUA criteria are based on preliminary results from the clinical trials that have evaluated these products. The details on the study designs, methods, and follow-up periods for these trials are currently limited. When peer-reviewed data from the Phase 3 trials become publicly available, the Panel will review the results and update the recommendations for using anti-SARS-CoV-2 mAbs if necessary.

Using Anti-SARS-CoV-2 Monoclonal Antibodies in Patients Hospitalized for COVID-19

The FDA EUAs do not authorize the use of anti-SARS-CoV-2 mAbs for the following patients:

- Those hospitalized for COVID-19; *or*
- Those who require oxygen therapy 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 because of COVID-19.

The FDA EUAs do permit the use of these agents 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.[13-15]

Anti-SARS-CoV-2 mAbs have been evaluated in hospitalized patients with severe COVID-19. A substudy of the ACTIV-3 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.[16,17]

There are now data that support the use of casirivimab 4,000 mg plus imdevimab 4,000 mg in hospitalized patients with COVID-19 who are seronegative for the anti-spike protein antibody. In the RECOVERY study, hospitalized patients with COVID-19 were randomized to receive standard of care with casirivimab 4,000 mg plus imdevimab 4,000 mg IV or standard of care alone. There was no difference in 28-day all-cause mortality between the casirivimab plus imdevimab arm and the standard of care arm; 944 of 4,839 patients (20%) in the casirivimab plus imdevimab arm died versus 1,026 of 4,946 patients (21%) in the standard of care arm (rate ratio 0.94; 95% CI, 0.86–1.03; $P = 0.17$). 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. 451 of 1,520 standard of care recipients [30%]; rate ratio 0.80; 95% CI, 0.70–0.91; $P = 0.001$).[18] This higher dose of casirivimab plus imdevimab is not available through the current EUA, and currently, casirivimab plus imdevimab 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.

SARS-CoV-2 Variants and Their 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 a number of the authorized anti-SARS-CoV-2 mAbs.[19] The clinical relevance of reduced in vitro susceptibility of select variants to anti-SARS-CoV-2 mAbs is under investigation.

Some of the key SARS-CoV-2 variants that have been identified are:

- *Alpha (B.1.1.7):* This variant retains in vitro susceptibility to all the anti-SARS-CoV-2 mAbs that are currently available through EUAs.[5,6]
- *Beta (B.1.351):* This variant includes the E484K and K417N mutations, which results in markedly reduced in vitro susceptibility to bamlanivimab and etesevimab.[5] In vitro studies also suggest that the Beta (B.1.351) variant has markedly reduced susceptibility to casirivimab, although the combination of casirivimab and imdevimab appears to retain activity against the variant. Sotrovimab also appears to retain activity against the variant.[6,7]
- *Gamma (P.1):* This variant includes the E484K and K417T mutations, which results in markedly reduced in vitro susceptibility to bamlanivimab and etesevimab.[5,20,21] The Gamma (P.1) variant also has reduced susceptibility to casirivimab; however, the combination of casirivimab plus imdevimab appears to retain activity against the variant. Sotrovimab also appears to retain activity against the Gamma (P.1) variant.[6,7]
- *Delta (B.1.617.2, non-AY.1/AY.2):* This is the predominant VOC circulating in the United States. This VOC retains in vitro susceptibility to all the anti-SARS-CoV-2 mAbs that are currently available through FDA EUAs.[5,6]

Table A. SARS-CoV-2 Variants and Susceptibility to Anti-SARS-CoV-2 Monoclonal Antibodies

WHO Label	Pango Lineage	CDC Variant Class	Notable Mutations	Bamlanivimab Plus Etesevimab		Casirivimab Plus Imdevimab		Sotrovimab	
				In Vitro Susceptibility[a]	Activity[b]	In Vitro Susceptibility[a]	Activity[b]	In Vitro Susceptibility[a]	Activity[b]
Alpha	B.1.1.7	VBM	N501Y	No change	Active	No change	Active	No change	Active
Beta	B.1.351	VBM	K417N, E484K, N501Y	Marked change	Unlikely to be active	No change[c]	Active	No change	Active
Gamma	P.1	VBM	K417T, E484K, N501Y	Marked change	Unlikely to be active	No change[c]	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

[a] Based on the fold reduction in susceptibility reported in the FDA EUAs.[5-7]

[b] Anticipated clinical activity against the variant, based on in vitro studies.

[c] Marked change for CAS and no change for IMD. The combination of CAS plus IMD appears to retain activity against the variant.

Key: CAS = casirivimab; CDC = Centers for Disease Control and Prevention; IMD = imdevimab; VOC = variant of concern; VBM = variant being monitored; WHO = World Health Organization

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 in defining the utility of specific mAbs in the future.

Clinical Trials

See Table 3a for information on the clinical trials that are evaluating the safety and efficacy of anti-SARS-CoV-2 mAbs in patients with COVID-19.

SARS-CoV-2 Vaccination

The CDC recommends that SARS-CoV-2 vaccination for people who have received anti-SARS-CoV-2 mAbs be deferred until ≥90 days after the therapy is completed. This is a precautionary measure, as the mAb treatment may interfere with vaccine-induced immune responses.[22]

For people who develop COVID-19 after SARS-CoV-2 vaccination, if there are no logistical or supply constraints limiting the availability of the authorized mAbs, prior vaccination should not affect decisions regarding the use and timing of mAb treatment.[22] For guidance on the use of anti-SARS-CoV-2 mAbs when there are logistical or supply constraints, see the Panel's updated statement on the prioritization of anti-SARS-CoV-2 mAbs.

Monitoring

The authorized anti-SARS-CoV-2 mAbs should be administered by IV infusion or SQ injections 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 infusion or SQ injections and for at least 1 hour after the infusion or injections are 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, dizziness, and pruritis have also been reported.[6,7,14] Injection site reactions, including ecchymosis and erythema, were reported in clinical trial participants who received casirivimab plus imdevimab by SQ administration.[6]

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 in the setting of 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 and/or prevention of COVID-19.

Considerations in Children

Please see Special Considerations in Children for therapeutic recommendations for children.

Drug Availability

Bamlanivimab plus etesevimab, casirivimab plus imdevimab, and sotrovimab are available through FDA EUAs. The availability of bamlanivimab plus etesevimab was previously restricted in areas with an elevated combined frequency of variants that have markedly reduced in vitro susceptibility to these agents (e.g., the Gamma and Beta variants). The FDA provides updated information on the distribution of bamlanivimab plus etesevimab in the United States. Efforts should be made to ensure that communities most affected by COVID-19 have equitable access to these mAbs.

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

Last Updated: October 19, 2021

This table describes only clinical trials that have evaluated anti-SARS-CoV-2 mAbs for the treatment of COVID-19. Please refer to the Prevention of SARS-CoV-2 Infection section for a discussion of 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, Phase 3 RCT of Bamlanivimab 700 mg Plus Etesevimab 1,400 mg in Nonhospitalized Patients With Mild to Moderate COVID-19[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:** • Proportion of patients with COVID-19-related hospitalization (defined as ≥24 hours of acute care) or all-cause death by Day 29	**Participant Characteristics:** • Median age 56 years; 30% ≥65 years; 53% female • 87% White; 27% Hispanic/Latinx; 8% Black/African American • Mean duration of symptoms was 4 days. • 76% had mild COVID-19 and 24% had 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 (6%) in placebo arm; relative risk difference: 87%; P <0.0001. • All-cause deaths by Day 29: 0 in BAM plus ETE arm vs. 4 (1.6%) in placebo arm; P = 0.01.	**Key Limitation:** • Trial results not yet published in peer-reviewed journal **Interpretation:** • Compared to placebo, receipt of BAM plus ETE was associated with 5% absolute reduction and 87% relative reduction in COVID-19-related hospitalizations or all-cause deaths.
BLAZE-1: Double-Blind, Phase 3 RCT of Bamlanivimab 2,800 mg Plus Etesevimab 2,800 mg in Nonhospitalized Patients With Mild to Moderate COVID-19[2]		
Key Inclusion Criteria: • Aged ≥12 years • At high risk for severe COVID-19 or hospitalization **Key Exclusion Criteria:** • SpO_2 ≤93% on room air, *or* • Respiratory rate ≥30 breaths/min, *or* • Heart rate ≥125 bpm **Interventions:** • Within 3 days of a positive SARS-CoV-2 test result, single infusion of: • BAM 2,800 mg plus ETE 2,800 mg (n = 518)	**Participant Characteristics:** • Mean age 53.8 years; 31% ≥65 years; 52% female; 48% male • 87% White; 29% Hispanic/Latinx; 8% Black/African American • Median days from symptom onset to infusion was 4 days. • 77% had mild COVID-19. **Primary Outcomes:** • COVID-19-related hospitalizations or all-cause deaths by Day 29: 11 (2.1%) in BAM plus ETE arm vs. 36 (7.0%) in placebo arm; relative risk difference: 70%; P < 0.001.	**Interpretation:** • Compared to placebo, receipt of BAM plus ETE was associated with 4.8% absolute reduction and 70% relative reduction in COVID-19-related hospitalizations or all-cause deaths.

Methods	Results	Limitations and Interpretation
BLAZE-1: Double-Blind, Phase 3 RCT of Bamlanivimab 2,800 mg Plus Etesevimab 2,800 mg in Nonhospitalized Patients With Mild to Moderate COVID-19[2], continued		
• Placebo (n = 517) **Primary Endpoint:** • Proportion of patients with COVID-19-related hospitalization or all-cause death by Day 29 **Secondary Endpoint:** • Proportion of patients with SARS-CoV-2 VL >5.27 $\log_{10}$ copies/mL at Day 7	• All-cause deaths by Day 29: 0 in BAM plus ETE arm vs. 10 (1.9%) in placebo arm. **Secondary Outcome:** • Proportion of patients with high VL at Day 7: 9.8% in BAM plus ETE arm vs. 29.5% in placebo arm ($P < 0.001$)	
Double-Blind, Phase 3 RCT of Casirivimab Plus Imdevimab in Nonhospitalized Patients With Mild to Moderate COVID-19[3]		
Key Inclusion Criteria: • Aged ≥18 years • Positive SARS-CoV-2 diagnostic test result • 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:** • Proportion of patients with COVID-19-related hospitalization or all-cause death through 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.	**Interpretation:** • Compared to placebo, receipt of CAS 600 mg plus IMD 600 mg was associated with 2.2% absolute reduction and 70% relative risk reduction in COVID-19-related hospitalizations or all-cause deaths. • Compared to placebo, receipt of CAS 1,200 mg plus IMD 1,200 mg was associated with 3.3% absolute reduction and 71% relative risk reduction in COVID-19-related hospitalizations or all-cause deaths.

Methods	Results	Limitations and Interpretation
COMET-ICE: Double-Blind, Phase 3 RCT of Sotrovimab in Nonhospitalized Patients With Mild to Moderate COVID-19 Interim Analysis[4]		
Key Inclusion Criteria: • Aged ≥18 years with ≥1 comorbidity or aged ≥55 years regardless of comorbidities • Laboratory-confirmed COVID-19 • Symptom onset ≤5 days before enrollment **Key Exclusion Criteria:** • Hospitalized or requiring supplemental oxygen • Severely immunocompromised **Interventions:** • SOT 500 mg IV (n = 291) • Placebo (n = 292) **Primary Endpoint:** • Proportion of patients with all-cause hospitalization or death by Day 29	**Participant Characteristics:** • Median age 53 years; 22% ≥65 years • 63% Hispanic/Latinx; 7% Black/African American **Primary Outcome:** • All-cause hospitalizations or deaths by Day 29: 3 (1%) in SOT arm vs. 21 (7%) in placebo arm (*P* = 0.002).	**Key Limitation:** • Trial results not yet published in peer-reviewed journal **Interpretation:** • Compared to placebo, receipt of SOT was associated with 6% absolute reduction and 85% relative risk reduction in all-cause hospitalizations or deaths.

Key: BAM = bamlanivimab; CAS = casirivimab; ETE = etesevimab; IMD = imdevimab; IV = intravenous; mAbs = anti-SARS-CoV-2 monoclonal antibodies; PEP = post-exposure prophylaxis; RCT = randomized controlled trial; RT-PCR = reverse transcription polymerase chain reaction; SOT = sotrovimab; SpO_2 = oxygen saturation; VL = viral load

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Convalescent Plasma

Last Updated: April 21, 2021

Plasma from donors who have recovered from COVID-19 may contain antibodies to SARS-CoV-2 that may help suppress the virus and modify the inflammatory response.[1] The Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for convalescent plasma for the treatment of certain hospitalized patients with COVID-19.

Recommendation

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of **low-titer COVID-19 convalescent plasma** for the treatment of COVID-19 **(AIIb)**.
  - Low-titer COVID-19 convalescent plasma is no longer authorized through the convalescent plasma EUA.

For Hospitalized Patients With COVID-19 Who Do Not Have Impaired Immunity

- The Panel **recommends against** the use of COVID-19 **convalescent plasma** for the treatment of COVID-19 in mechanically ventilated patients **(AI)**.
- The Panel **recommends against** the use of **high-titer COVID-19 convalescent plasma** for the treatment of COVID-19 in hospitalized patients who do not require mechanical ventilation, except in a clinical trial **(AI)**.

For Hospitalized Patients With COVID-19 Who Have Impaired Immunity

- There is insufficient evidence for the Panel to recommend either for or against the use of high-titer COVID-19 convalescent plasma for the treatment of COVID-19.
  - Observational data including data from case reports, case series, and a retrospective case control study suggest a benefit of COVID-19 convalescent plasma in patients with various primary and secondary humoral immunodeficiencies.[2-16]
  - Several case reports indicate that patients with impaired humoral immunity may experience persistent SARS-CoV-2 viral replication and therefore, may be at risk for developing viral resistance to SARS-CoV-2 antibodies after treatment with COVID-19 convalescent plasma.[17-19]
  - High-titer convalescent plasma is authorized under the EUA for the treatment of hospitalized patients with COVID-19 and impaired immunity.

For Nonhospitalized Patients With COVID-19

- There is insufficient evidence for the Panel to recommend either for or against the use of high-titer COVID-19 convalescent plasma for the treatment of COVID-19 in patients who are not hospitalized, except in a clinical trial.
  - Convalescent plasma is not authorized for nonhospitalized patients with COVID-19 under the EUA.
  - Results from additional adequately powered, well-designed, and well-conducted randomized clinical trials are needed to provide more specific, evidence-based guidance on the role of COVID-19 convalescent plasma in the treatment of nonhospitalized patients with COVID-19.

Rationale for Recommendation

On August 23, 2020, the FDA issued an EUA for convalescent plasma for the treatment of hospitalized patients with COVID-19 based on retrospective, indirect evaluations of efficacy generated from a large Expanded Access Program (EAP). The EAP allowed for the use of convalescent plasma regardless of titer. The Panel reviewed the EAP analyses and determined that the data were not sufficient to establish the efficacy or safety of COVID-19 convalescent plasma due to potential confounding, the lack of randomization, and the lack of an untreated control group.

On February 4, 2021, the FDA revised the convalescent plasma EUA to limit the authorization to high-titer COVID-19 convalescent plasma and only for the treatment of hospitalized patients with COVID-19 early in the disease course or hospitalized patients who have impaired humoral immunity.

Use of Convalescent Plasma in Hospitalized Patients With COVID-19 and Without Impaired Humoral Immunity

An updated retrospective analysis of data collected through the EAP indicated that patients who received high-titer plasma had a lower relative risk of death within 30 days after transfusion than patients who received low-titer plasma (relative risk 0.82; 95% CI, 0.67–1.00).[20]

- Among the patients who were on mechanical ventilation before transfusion, no effect of high-titer plasma versus low-titer plasma was observed (relative risk 1.02; 95% CI, 0.78–1.32).
- Among the patients who were not on mechanical ventilation before transfusion, mortality was lower among patients who received high-titer plasma than among those who received low-titer plasma (relative risk 0.66; 95% CI, 0.48–0.91).[20]

The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial is an open-label, randomized controlled platform trial evaluating potential treatments for COVID-19. In the convalescent plasma portion of the trial, 11,558 patients were randomized to receive either convalescent plasma (n = 5,795) or usual care (n = 5,763) before enrollment was stopped due to futility.[21]

The trial results demonstrated no significant differences in the primary endpoint of 28-day mortality between the convalescent plasma arm (24%) and the usual care arm (24%; risk ratio 1.00; 95% CI, 0.93–1.07). Additionally, the trial did not meet its two secondary endpoints: time to hospital discharge and, for those not on mechanical ventilation at randomization, receipt of invasive mechanical ventilation or death. The proportion of patients discharged within 28 days was similar in the convalescent plasma arm and the usual care arm (66% vs. 67%; rate ratio 0.98; 95% CI, 0.94–1.03). Among those not requiring invasive mechanical ventilation at baseline, the proportion of those progressing to invasive mechanical ventilation or death was also similar in the convalescent plasma arm and the usual care arm (28% vs. 29%; risk ratio 0.99; 95% CI, 0.93–1.05). The 28-day mortality rate ratio was similar in all prespecified patient subgroups, including in those patients without detectable SARS-CoV-2 antibodies at randomization (32% in the convalescent plasma arm vs. 34% in the usual care arm; rate ratio 0.94; 95% CI, 0.84–1.06). Subgroup analyses suggested a slight trend towards benefit of convalescent plasma in certain subgroups (e.g., those with symptom onset ≤7 days, no requirement for supplemental oxygen at baseline, no concomitant use of corticosteroids). See Table 3b for additional details.

Data from several other randomized clinical trials, all of which were underpowered, have not demonstrated the efficacy of convalescent plasma for the treatment of hospitalized patients with COVID-19.[22-29] See Table 3b for details.

Additionally, two large, randomized trials evaluating convalescent plasma in hospitalized patients have been paused or have limited enrollment due to futility.

- The CONvalescent Plasma for Hospitalized Adults With COVID-19 Respiratory Illness (CONCOR-1) trial, which evaluated convalescent plasma versus usual care, was stopped after an interim analysis of 614 patients met the predefined threshold for futility.[30]
- The Randomised, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP), which evaluated convalescent plasma in hospitalized patients, paused enrollment for patients in intensive care units after a preliminary analysis that included 912 participants indicated that convalescent plasma was unlikely to benefit this patient group.[31] REMAP-CAP continues to recruit hospitalized patients who do not require intensive care support into the trial's convalescent plasma evaluation domain.

Results from adequately powered, well-designed, and well-conducted randomized clinical trials are needed to provide more specific, evidence-based guidance on the role of convalescent plasma in the treatment of hospitalized patients with COVID-19 who do not have impaired humoral immunity.

Use of Convalescent Plasma in Hospitalized Patients With COVID-19 and Impaired Humoral Immunity

Data from case reports, case series, and a retrospective case-control study suggest a benefit of convalescent plasma in patients with primary and secondary humoral immunodeficiencies, including patients with hematologic malignancy, common variable immune deficiency, and agammaglobulinemia, and those who have received a transplanted solid organ.[2-13,15,16] Several case reports indicate that patients with impaired humoral immunity may experience persistent SARS-CoV-2 viral replication and, therefore, may be at risk for developing viral resistance to SARS-CoV-2 antibodies after treatment with convalescent plasma.

Results from adequately powered, well-designed, and well-conducted randomized clinical trials are needed to provide more specific, evidence-based guidance on the role of convalescent plasma in the treatment of patients with COVID-19 who have impaired humoral immunity.[17-19]

Use of Convalescent Plasma in Nonhospitalized Patients With COVID-19

Current data are insufficient to establish the safety or efficacy of convalescent plasma in outpatients with COVID-19.

- Data from a double-blind, placebo-controlled randomized trial of high-titer convalescent plasma in elderly outpatients with <72 hours of mild COVID-19 symptoms suggested a potential for benefit.[32] However, the trial included relatively few participants, and only a small number of clinical events related to COVID-19 occurred. See Table 3b for details.
- The Clinical Trial of COVID-19 Convalescent Plasma of Outpatients (C3PO) evaluated convalescent plasma for the treatment of nonhospitalized patients with ≤7 days of mild or moderate COVID-19 symptoms and at least one risk factor for severe COVID-19. The trial was halted after an interim analysis indicated no benefit of convalescent plasma for this group of patients. The trial enrolled 511 of the planned 900 participants before the study was halted.

Convalescent plasma is not authorized for nonhospitalized patients with COVID-19 under the EUA.

Clinical Data to Date

Table 3b includes a summary of key studies of convalescent plasma for the treatment of COVID-19.

Considerations in Pregnancy

The safety and efficacy of using COVID-19 convalescent plasma during pregnancy have not been evaluated. Pathogen-specific immunoglobulins 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.[33] Some ongoing clinical trials that are evaluating COVID-19 convalescent plasma include pregnant individuals.[34]

Considerations in Children

The safety and efficacy of COVID-19 convalescent plasma have not been evaluated in pediatric patients outside of evaluations described in single-center reports. Clinical trials of COVID-19 convalescent plasma in children are ongoing. 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 hospitalized children who do not require mechanical ventilation. The Panel **recommends against** the use of **convalescent plasma** for the treatment of COVID-19 in mechanically ventilated pediatric patients **(AIII)**. In consultation with a pediatric infectious disease specialist, high-titer convalescent plasma may be considered on a case-by-case basis for children with COVID-19 who meet the EUA criteria.

Adverse Effects

Available data suggest that serious adverse reactions following the administration of COVID-19 convalescent plasma are infrequent and consistent with the risks associated with plasma infusions for other indications. These risks include transfusion-transmitted infections (e.g., 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.[21,35,36]

Additional risks of COVID-19 convalescent plasma transfusion include a theoretical risk of antibody-dependent enhancement of SARS-CoV-2 infection and a theoretical risk of long-term immunosuppression.

The Panel recommends consulting a transfusion medicine specialist when considering convalescent plasma for patients with a history of severe allergic or anaphylactic transfusion reactions.

Product Availability

On February 4, 2021, the FDA revised the convalescent plasma EUA to limit the authorization to high-titer COVID-19 convalescent plasma.[37]

- The revised EUA Letter of Authorization provides an expanded list of anti-SARS-CoV-2 antibody tests and corresponding qualifying results that may be used to determine the suitability of donated convalescent plasma.
- Please refer to the FDA's Recommendations for Investigational COVID-19 Convalescent Plasma webpage for guidance on the transfusion of investigational convalescent plasma while blood establishments develop the necessary operating procedures to manufacture COVID-19 convalescent plasma in accordance with the Conditions of Authorization described in the EUA.[38]

Clinical Trials

Randomized clinical trials that are evaluating convalescent plasma 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 21, 2021

The clinical trials described in this table do not represent all the trials that the Panel reviewed while developing the recommendations for COVID-19 CP. The studies summarized below are those that have had the greatest impact on the Panel's recommendations.

Study Design	Methods	Results	Limitations and Interpretation
Convalescent Plasma in Hospitalized Patients With COVID-19 (RECOVERY Trial)[1]			
Open-label, platform RCT evaluating potential treatments, including high-titer CP, in hospitalized patients with COVID-19 in the United Kingdom (n = 11,558) *This is a preliminary report that has not yet been peer reviewed.*	**Key Inclusion Criteria:** • Clinically suspected or laboratory-confirmed SARS-CoV-2 infection • CP available at study site **Key Exclusion Criteria:** • CP contraindicated (e.g., known allergy to blood components) **Interventions:** • One 275 mL (+/- 75 mL) unit of CP immediately and another unit the next day (≥12 hours after the first unit) • CP was selected by sample to cut-off IgG SARS-CoV-2 spike protein ratio ≥6.0. • Usual care **Primary Endpoint:** • All-cause mortality at Day 28 **Secondary Endpoints:** • Time to hospital discharge • Among patients not receiving IMV at randomization, receipt of IMV or death by Day 28	**Number of Participants:** • ITT analysis: CP (n = 5,795) and usual care (n = 5,763) **Participant Characteristics:** • Mean age was 63.5 years. • 63% of patients in the CP arm and 66% in the usual care arm were men. • 5% of patients in each arm were on IMV. • At baseline, 52% of the patients in the CP arm and 48% in the usual care arm were SARS-CoV-2 antibody seropositive. • 93% of the patients in the CP arm and 92% in the usual care arm received corticosteroids. **Outcomes:** • No difference in 28-day mortality between the CP arm and the usual care arm (24% vs. 24%; rate ratio 1.00; 95% CI, 0.93–1.07). • No difference in the proportion of patients discharged within 28 days (66% in CP arm vs. 67% in usual care arm; rate ratio 0.98; 95% CI, 0.94–1.03; *P* = 0.50). • 28-day mortality rate ratio was consistent across prespecified patient subgroups, including subgroups by SARS-CoV-2 antibody presence at randomization. In particular, among patients without detectable SARS-CoV-2 antibodies, there was no evidence of a mortality difference between those who received CP and those who received usual care (32% vs. 34%; rate ratio 0.94; 95% CI, 0.84–1.06). • Among those not receiving IMV at baseline, the percentage of patients who progressed to IMV or died was similar in the CP arm and the usual care arm (28% vs. 29%; rate ratio 0.99; 95% CI, 0.93–1.05; *P* = 0.79). • Severe allergic reactions were rare (occurred in 16 patients in the CP arm and 2 in the usual care arm).	**Limitations:** • The study was not blinded. • >90% of participants received corticosteroids. There is uncertainty about the effect of CP in hospitalized patients who do not require supplemental oxygen and for whom corticosteroids are not recommended. **Interpretation:** • The trial did not demonstrate a benefit of CP in hospitalized patients with COVID-19.

Study Design	Methods	Results	Limitations and Interpretation
Convalescent Plasma in Hospitalized Adults With COVID-19 (PLACID Trial)[2]			
Multicenter, open-label, Phase 2 RCT in hospitalized adults with severe COVID-19 in India (n = 464)	**Key Inclusion Criteria:** • Aged ≥18 years • Positive SARS-CoV-2 RT-PCR • PaO_2/FiO_2 = 200–300 mm Hg or respiratory rate >24 breaths/min with SpO_2 ≤93% on room air **Key Exclusion Criteria:** • Critical illness **Interventions:** • 2 doses of 200 mL CP, transfused 24 hours apart • SOC **Primary Endpoint:** • Composite of progression to severe disease (defined as PaO_2/FiO_2 <100 mm Hg) any time within 28 days of enrollment or all-cause mortality at 28 days	**Number of Participants:** • CP (n = 235) and SOC (n = 229) **Participant Characteristics:** • Median age was 52 years. • 75% of participants in the CP arm and 77% in the SOC arm were men. • Higher prevalence of diabetes in the CP arm (48%) than in SOC arm (38%). **Outcomes:** • No difference between the arms in the primary outcome of progression to severe disease or death (occurred in 18.7% of participants in CP arm and 17.9% in SOC arm). • A post hoc analysis evaluating outcomes among patients without detectable SARS-CoV-2 neutralizing antibody titers at baseline also revealed no benefit of CP.	**Limitations:** • The study was not blinded. • SARS-CoV-2 antibody testing was not used to select donated CP units; therefore, many participants may have received CP units with low titers of SARS-CoV-2 neutralizing antibodies. **Interpretation:** • This trial did not demonstrate a benefit of CP in hospitalized patients with severe COVID-19.
Convalescent Plasma in COVID-19 Severe Pneumonia (PlasmAr Study)[3]			
Double-blind, placebo-controlled, multicenter RCT in hospitalized adults with severe COVID-19 in Argentina (n = 333)	**Key Inclusion Criteria:** • Aged ≥18 years • Positive SARS-CoV-2 RT-PCR • Severe COVID-19 **Key Exclusion Criteria:** • Critical illness **Interventions** *2:1 Randomization:* • Single dose (median volume	**Number of Participants:** • CP (n = 228) and placebo (n = 105) **Participant Characteristics:** • Median age was 62 years. • 67.6% of the participants were men. • 64.9% of the participants had a coexisting condition at trial entry. • Median time from symptom onset to enrollment was 8 days. • Of 215 participants tested, 46% had no detectable SARS-CoV-2 antibodies at baseline. Median SARS-CoV-2 antibody titer in both the CP arm and placebo arm was 1:50.	**Limitations:** • The majority of participants in both arms received concomitant glucocorticoid treatment, potentially masking subtle differences in clinical outcomes between the study arms.

Study Design	Methods	Results	Limitations and Interpretation
Convalescent Plasma in COVID-19 Severe Pneumonia (PlasmAr Study)[3], continued			
	500 mL) of CP pooled from 2–5 donors. Only plasma units with a SARS-CoV-2 viral spike-RBD IgG titer ≥1:800 were transfused. • Placebo **Primary Endpoint:** • Change in clinical status 30 days after intervention measured using a 6-point ordinal scale	**Outcomes:** • No significant differences between the arms in the distribution of outcomes according to the categories on the 6-point ordinal scale (OR 0.83; 95% CI, 0.52–1.35). • 30-day mortality was similar in CP arm (11.0%) and placebo arm (11.4%). • Infusion-related AEs were more frequent in the CP arm than in the placebo arm (occurred in 4.8% vs. 1.9% of participants).	**Interpretation:** • This trial did not demonstrate a benefit of CP in hospitalized patients with severe COVID-19.
Convalescent Plasma in Adults With Severe COVID-19[4]			
Double-blind, Phase 2 RCT in hospitalized adults with severe COVID-19 (n = 223) in the United States (n = 73) and Brazil (n = 150) *This is a preliminary report that has not yet been peer reviewed.*	**Key Inclusion Criteria:** • Aged ≥18 years • COVID-19 pneumonia • SpO_2 ≤94% on room air or requirement for supplemental oxygen, IMV, or ECMO **Key Exclusion Criteria:** • >5 days on IMV or ECMO • Severe multiorgan failure **Interventions** *2:1 Randomization:* • Single dose of SARS-CoV-2 CP (approximately 250 mL). Only units with a SARS-CoV-2 viral spike-RBD IgG titer ≥1:400 were transfused. • Non-SARS-CoV-2 plasma (normal control plasma)	**Number of Participants:** • CP (n = 150) and normal control plasma (n = 73) • Enrollment initiated in New York City in April 2020 and in Brazil in August 2020 **Participant Characteristics:** • Median age was 61 years. • 66% of the participants were men. • Median duration of symptoms prior to randomization was 9 days. • 57% of the participants required supplemental oxygen at baseline, 25% required high-flow oxygen or noninvasive ventilation, and 13% required IMV or ECMO. • There were some imbalances between the study arms at baseline. The CP arm included more women; the participants were younger and had slightly longer symptom durations. • 81% of the participants received corticosteroids. **Outcomes:** • No difference in clinical status on Day 28 was observed between the CP arm and the control arm (OR 1.5 for being in a better category with CP vs. control plasma; 95% CI, 0.83–2.68; $P = 0.18$).	**Limitations:** • The intervention in the control group arm was blood plasma without SARS-CoV-2 antibodies. This ensured blinded administration; however, because the trial was not placebo controlled; it is not possible to identify potential harm due to plasma infusion. • Low sample size and number of events • There were imbalances in baseline characteristics between the study arms that may have impacted study outcomes. After adjustment for the imbalances, the

Study Design	Methods	Results	Limitations and Interpretation
Convalescent Plasma in Adults With Severe COVID-19[4], continued			
	Primary Endpoint: • Clinical status on Day 28, measured using an ordinal scale (initially with 7 categories, but modified to 6). **Secondary Endpoints:** • Time to clinical improvement • In-hospital and 28-day mortality • Time to discontinuation of supplemental oxygen • Time to hospital discharge	• In-hospital mortality was lower in the CP arm (13%) than in the control arm (25%; HR 0.44; 95% CI, 0.22–0.91; $P = 0.034$). The treatment difference was not significant after adjustment for age, sex, and duration of symptoms at baseline. • In both arms, mortality at 28 days was the same as in-hospital mortality. • Time to oxygen discontinuation and time to hospital discharge were similar between the arms. • 25.5% of patients in the CP arm vs. 36.1% in the control arm experienced SAEs.	difference in mortality between the arms was not significant. • The treatment difference in the primary outcome (clinical status on Day 28) was not statistically significant; mortality was a secondary outcome. • There were no subgroup analyses for mortality. **Interpretation:** • Although the difference between the CP arm and the non-SARS-CoV-2 antibody plasma arm for the primary outcome of clinical status on Day 28 was not statistically significant, the lower 28-day mortality in the CP arm suggests a potential benefit of CP in hospitalized patients with severe COVID-19.

Study Design	Methods	Results	Limitations and Interpretation
Early High-Titer Plasma Therapy to Prevent Severe COVID-19 in Older Adults[5]			
Double-blind, placebo-controlled RCT in outpatients with mild COVID-19 in Argentina (n = 160)	**Key Inclusion Criteria:** • Aged >75 years or aged 65–74 years with ≥1 coexisting condition • Outpatient with <72 hours of mild COVID-19 symptoms **Key Exclusion Criteria:** • Severe respiratory disease **Interventions:** • Single 250 mL dose of CP with an IgG titer against SARS-CoV-2 spike protein of >1:1000 • Placebo **Primary Endpoint:** • Severe respiratory disease defined as a respiratory rate ≥30 breaths/min and/or SpO_2 <93% on room air by Day 15	**Number of Participants:** • ITT analysis: CP (n = 80) and placebo (n = 80) **Participant Characteristics:** • Mean age was 77 years. • Most of the patients had comorbidities. **Outcomes:** • 13 of 80 patients (16%) in the CP arm and 25 of 80 (31%) in the placebo arm experienced severe respiratory disease by Day 15 (relative risk 0.52; 95% CI, 0.29–0.94; *P* = 0.026). • 2 participants in the CP arm and 5 in the placebo arm died. • No solicited AEs were reported.	**Limitations:** • The trial was terminated early because cases of COVID-19 at the study site decreased. • The trial included relatively few participants. **Interpretation:** • This trial demonstrated a benefit of CP in elderly outpatients with <72 hours of mild COVID-19 symptoms.
Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-Threatening COVID-19[6]			
Multicenter, open-label, randomized trial in hospitalized adults with severe or life-threatening COVID-19 in China (n = 103)	**Key Inclusion Criteria:** • Aged ≥18 years • Positive SARS-CoV-2 PCR within 72 hours of randomization • Met study definition of severe or life-threatening COVID-19	**Number of Participants:** • CP (n = 52) and SOC (n = 51) **Participant Characteristics:** • Median age was 70 years. • 58.3% of the participants were men. **Outcomes:** • No significant difference in time to clinical improvement between the CP arm and the control arm (HR 1.40; 95% CI, 0.79–2.49; *P* = 0.26). • No significant difference in mortality between the CP arm (16%) and the control arm (24%; *P* = 0.30).	**Limitations:** • The study was not blinded. • The trial was stopped early because of decreasing numbers of cases of COVID-19 at the study site; therefore, the study lacked sufficient power to detect differences in clinical outcomes.

Study Design	Methods	Results	Limitations and Interpretation
Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-Threatening COVID-19[6], continued			
	Key Exclusion Criteria: • Baseline RBD-specific IgG antibody ≥1:64 • Certain sequalae of severe COVID-19 (e.g., severe septic shock, severe heart failure) **Interventions:** • Single 4–13 mL/kg dose of CP. Only CP units with a SARS-CoV-2 viral spike-RBD-specific IgG titer of ≥1:640 were transfused. • SOC **Primary Endpoint:** • Time to clinical improvement (patient discharge or a reduction of 2 points on a 6-point disease severity scale; 6 points = death, 1 point = hospital discharge) within 28 days.		• Only 103 of 200 planned participants were randomized to receive treatment. • CP was administered late (approximately 1 month) into disease course. **Interpretation:** • This trial did not demonstrate a benefit of CP in hospitalized patients with severe or life-threatening COVID-19.
Early Versus Deferred Anti-SARS-CoV-2 Convalescent Plasma in Hospitalized Patients With COVID-19[7]			
Open-label, single-center, Phase 2 randomized trial in hospitalized adults with COVID-19 in Chile (n = 58)	**Key Inclusion Criteria:** • Aged ≥18 years • ≤7 days of COVID-19 symptoms • High risk of progression to respiratory failure **Key Exclusion Criteria:** • PaO_2/FiO_2 <200 mm Hg • Mechanical ventilation	**Number of Participants:** • Immediate CP (n = 28) and deferred CP (n = 30) **Participant Characteristics:** • Median age was 66 years. • 50% of the participants were men. • Median interval between symptom onset and randomization was 6 days. • 13 of 28 participants (43%) in the deferred CP arm received CP at a median of 3 days after enrollment.	**Limitations:** • The study was not blinded. • Small sample size. **Interpretation:** • This trial did not demonstrate a benefit of immediate vs. deferred administration of CP in hospitalized COVID-19 patients with ≤7 days of COVID-19 symptoms.

Study Design	Methods	Results	Limitations and Interpretation
Early Versus Deferred Anti-SARS-CoV-2 Convalescent Plasma in Hospitalized Patients With COVID-19[7], continued			
	Interventions *Immediate CP:* • Two 400 mL doses of CP with anti-SARS-CoV-2 neutralizing antibody titers ≥1:400, transfused 24 hours apart *Deferred CP:* • CP transfusion only if PaO_2/FiO_2 <200 mm Hg, or if participant still required hospitalization for COVID-19 symptoms 7 days after enrollment **Primary Endpoint:** • Composite of mechanical ventilation, hospitalization >14 days, or in-hospital death	**Outcomes:** • There was no difference between the arms in the percentage of participants who met the primary composite endpoint of death, mechanical ventilation, or >14 days hospitalization (32% in immediate CP arm vs. 33% in deferred CP arm; OR 0.95; 95% CI, 0.32–2.84). • 18% of participants in the immediate CP arm vs. 7% in the deferred CP arm died within 30 days (OR 3.0; 95% CI, 0.5–17.2; *P* = 0.25).	
Convalescent Plasma for COVID-19 (ConCOVID trial)[8]			
Multicenter, open-label, RCT in hospitalized adults with COVID-19 in the Netherlands (n = 86) *This is a preliminary report that has not yet been peer reviewed.*	**Key Inclusion Criteria:** • Aged ≥18 years • Clinical disease with positive SARS-CoV-2 RT-PCR within 96 hours of enrollment **Key Exclusion Criteria:** • Mechanical ventilation for >96 hours **Interventions:** • One to two 300 mL doses of CP with anti-SARS-CoV-2 neutralizing antibody titers ≥1:80 • SOC	**Number of Participants:** • CP (n = 43) and SOC (n = 43) **Participant Characteristics:** • Median age was 63 years. • Most of the participants were men. **Outcomes:** • No differences in mortality (*P* = 0.95), length of hospital stay (*P* = 0.68), or disease severity at Day 15 (*P* = 0.58) were observed between the study arms.	**Limitations:** • The study was not blinded. • Trial halted early by the investigators when the baseline SARS-CoV-2 neutralizing antibody titers of participant plasma and CP were found to be comparable, challenging the potential benefit of CP for the study population. Thus, the study lacked sufficient power to detect differences in clinical outcomes between the study arms.

Study Design	Methods	Results	Limitations and Interpretation
Convalescent Plasma for COVID-19 (ConCOVID trial)[8], continued			
	Primary Endpoint: • Day-60 mortality		• Only 86 of 426 planned participants were randomized to receive CP or SOC. **Interpretation:** • This trial did not demonstrate a benefit of COVID-19 CP in hospitalized patients.
Convalescent Plasma for COVID-19 (ConPlas-19 Study)[9]			
Multicenter, open-label, RCT in hospitalized adults with COVID-19 in Spain (n = 81) *This is a preliminary report that has not yet been peer reviewed.*	**Key Inclusion Criteria:** • Aged ≥18 years **Key Exclusion Criteria:** • Receiving IMV, noninvasive ventilation, or high-flow oxygen **Interventions:** • Single dose of 250–300 mL of CP plus SOC. • All administered units had neutralizing antibodies (VMNT-ID50: all titers >1:80, median titer 1:292, IQR 238–451; pseudovirus neutralizing ID50 assay: median titer 1:327; IQR 168–882) • SOC alone **Primary Endpoint:** • Proportion of patients in ordinal scale categories 5, 6, or 7 at Day 15.	**Number of Participants:** • CP (n = 38) and SOC (n = 43) **Participant Characteristics:** • Mean age was 59 years. • At baseline, 49% of the participants were SARS-CoV-2 antibody positive. **Outcomes:** • 0 of 38 participants (0%) in the CP arm progressed to ordinal scale categories 5–7 vs. 6 of 43 participants (14.0%) in the SOC arm (P = 0.57, not statistically significant according to the planned analysis; but P = 0.03 using Fisher test as a post hoc sensitivity analysis given small numbers and the by-center heterogenous distribution). • 0 of 38 participants (0%) in the CP arm died vs. 4 of 43 (9.3%) in the SOC arm (P = 0.06).	**Limitations:** • The study was not blinded. • The trial was stopped early because of decreasing numbers of COVID-19 cases at the study site and, thus, the study lacked sufficient power to detect differences in clinical outcomes. • Only 81 of planned 278 participants were enrolled. **Interpretation:** • Although the results did not reach statistical significance and only a small number of clinical events related to COVID-19 occurred, these results suggest a potential benefit of CP in hospitalized patients who are not receiving high-flow oxygen, noninvasive ventilation, or invasive ventilation.

Study Design	Methods	Results	Limitations and Interpretation
Clinical and Immunological Benefits of Convalescent Plasma Therapy in Severe COVID-19[10]			
Single-center, open-label, RCT in hospitalized adults with COVID-19 and ARDS in India (n = 80) *This is a preliminary report that has not yet been peer reviewed.*	**Key Inclusion Criteria:** • Evidence of ARDS (defined as PaO_2/FiO_2 100–300 mm Hg) • Not on mechanical ventilation **Key Exclusion Criteria:** • Mechanical ventilation **Intervention:** • 2 consecutive doses of ABO-matched 200 mL CP, 1 day apart • SOC alone **Primary Endpoint:** • All-cause mortality at Day 30	**Number of Participants:** • CP (n = 40) and SOC (n = 40) **Participant Characteristics:** • Mean age was 61 years. • 71% of the participants were men. • No difference in mean number of days of hospitalization at enrollment between the CP arm (4.2 days) and the SOC arm (3.9 days). **Outcomes**: • 10 of 40 participants (25%) in the CP arm had died by Day 30 vs. 14 of 40 (35%) in the SOC arm. • Difference in survival between the arms was not statistically significant (HR 0.6731; 95% CI, 0.3010–1.505).	**Limitations**: • The study was not blinded. • The study lacked sufficient power to detect differences in clinical outcomes between the study arms. **Interpretation**: • This trial did not demonstrate a benefit of CP in hospitalized patients with mild to moderate ARDS who are not receiving mechanical ventilation.
Convalescent Plasma Therapy Versus Standard Therapy in Patients With Severe COVID-19[11]			
Open-label, RCT in hospitalized adults with COVID-19 in Bahrain (n = 40) *This is a preliminary report that has not yet been peer reviewed.*	**Key Inclusion Criteria:** • Aged ≥21 years • Radiologic evidence of pneumonia • Requirement for oxygen therapy for COVID-19 **Key Exclusion Criteria:** • Requirement for IMV, noninvasive ventilation, or high-flow oxygen **Interventions:** • Two 200 mL transfusions of CP over 24 hours • SOC alone **Primary Endpoints:** • Requirement for IMV or noninvasive ventilation	**Number of Participants:** • CP (n = 20) and SOC (n = 20) **Participant Characteristics:** • Mean age was 53 years in the CP arm and 51 years in the SOC arm. • Most of the participants were men (75% in the CP arm and 85% in the SOC arm). **Outcomes:** • 6 patients in the SOC arm and 4 patients in the CP arm required mechanical ventilation (risk ratio 0.67; 95% CI, 0.22–2.0; P = 0.72). • 2 patients in the SOC arm died vs. 1 in the CP arm.	**Limitations:** • The study was not blinded. • The study lacked sufficient power to detect differences in clinical outcomes between the study arms. **Interpretation:** • This trial did not demonstrate a benefit of CP in hospitalized patients who are not receiving high-flow oxygen, noninvasive ventilation, or invasive ventilation.

Study Design	Methods	Results	Limitations and Interpretation
Convalescent Plasma Therapy Versus Standard Therapy in Patients With Severe COVID-19[11], continued			
	• In patients who require ventilation, duration of ventilation		
Convalescent Plasma Antibody Levels and the Risk of Death from COVID-19[12]			
Retrospective, indirect evaluation of a subset of patients from the Mayo Clinic COVID-19 CP EAP (n = 3,082). More than 100,000 patients hospitalized with COVID-19 in the United States received CP through the Mayo Clinic EAP.	**Key Inclusion Criteria:** • Aged ≥18 years • Severe or life-threatening (critical) COVID-19 • Analysis limited to patients for whom samples were available for retrospective analysis of CP titer. **Intervention:** • CP transfusion (no titer specified in real time; high, medium, and low titer CP determined retrospectively) **Primary Endpoint:** • Mortality 30 days after CP transfusion	**Number of Participants:** • High-titer CP (n = 515), medium-titer CP (n = 2,006), and low-titer CP (n = 561) **Participant Characteristics:** • 61% of the participants were men. • 48% of the participants were White and 37% were Hispanic/Latino. • 61% of the participants required ICU-level care prior to infusion. • 33% of the participants were on mechanical ventilation. • 51% of the participants received corticosteroids; 31% received RDV. **Outcomes:** • The analysis included 3,082 participants who received a single unit of CP. The participants were among 35,322 participants who had received CP through the EAP by July 4, 2020. • Death within 30 days occurred in 115 of 515 patients (22%) in the high-titer group, 549 of 2,006 patients (27%) in the medium-titer group, and 166 of 561 patients (30%) in the low-titer group. • Using a relative-risk regression model that assumed all patients who were discharged were alive at Day 30, patients in the high-titer group had a lower relative risk of death within 30 days than patients in the low-titer group (relative risk 0.82; 95% CI, 0.67–1.00). • Among patients who received mechanical ventilation before transfusion, there was no difference in the risk of death between those who received high-titer CP and those who received low-titer CP (relative risk 1.02; 95% CI, 0.78–1.32). • Mortality was lower among patients who were not receiving mechanical ventilation before transfusion (relative risk 0.66; 95% CI, 0.48–0.91).	**Limitations:** • Lack of untreated control arm limits interpretation of the safety and efficacy data; the possibility that differences in outcomes are attributable to harm from low-titer plasma rather than benefit from high-titer plasma cannot be excluded. • Assays to determine the effective antibody titers remain limited, and the antibody titers of currently available CP from COVID-19 survivors are highly variable. • Efficacy analysis relied on only a subset of EAP patients who represent a fraction of the patients who received CP through the EAP. • Post hoc subgroups were selected by combining several subsetting rules that favored subgroups. This approach tends to overestimate the treatment effect. **Interpretation:** • Given the lack of an untreated control arm and the limitations listed above, this retrospective analysis is not sufficient to establish the efficacy or safety of CP.

Key: AE = adverse event; ARDS = acute respiratory distress syndrome; ConCOVID Trial = Convalescent-plasma-for-COVID-9; ConPlas-19 Study = Convalescent Plasma for COVID-19; CP = convalescent plasma; EAP = Expanded Access Program; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; ID50 = 50% inhibitory dose; IgG = immunoglobulin G; IMV = invasive mechanical ventilation; ITT = intention to treat; the Panel = the COVID-19 Treatment Guidelines Panel; PaO_2/FiO_2 = ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; PCR = polymerase chain reaction; PLACID Trial = Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomized controlled trial; PlasmAr Study = A Randomized Trial of Convalescent Plasma in COVID-19 Severe Pneumonia; RBD = receptor binding domain; RCT = randomized controlled trial; RDV = remdesivir; RECOVERY = Randomised Evaluation of COVID-19 Therapy; RT-PCR = reverse transcriptase polymerase chain reaction; SAE = serious adverse event; SOC = standard of care; SpO_2 = saturation of oxygen; VMNT = virus microneutralization test

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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.

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

Last Updated: October 19, 2021

- 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)				
Dose Recommended in EUA for Treatment and PEP of COVID-19: • BAM 700 mg plus ETE 1,400 mg administered together 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 patient during the IV infusion and for at least 1 hour after the 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:** • The distribution of BAM plus ETE in the United States was paused in June 2021 because the Gamma (P.1) and Beta (B.1.351) variants have reduced susceptibility to BAM and ETE. Distribution of BAM plus ETE was resumed in August 2021. • For updates on the distribution of BAM plus ETE, see this FDA document.

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				
				• BAM plus ETE is available through the FDA EUA as treatment for high-risk outpatients with mild to moderate COVID-19 and as PEP for certain high-risk patients.[1] See Anti-SARS-CoV-2 Monoclonal Antibodies and Prevention of SARS-CoV-2 Infection for a list of high-risk conditions and criteria for use of BAM plus ETE. • A list of clinical trials is available: Bamlanivimab Plus Etesevimab
Casirivimab Plus Imdevimab (Anti-SARS-CoV-2 Monoclonal Antibodies)				
Dose Recommended in EUA for Treatment of COVID-19: • CAS 600 mg plus IMD 600 mg administered together 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 SQ injections (2.5 mL per injection) at 4 different sites. See the FDA EUA for detailed information. **Dose Recommended in EUA for PEP of COVID-19:** • CAS 600 mg plus IMD 600 mg administered by SQ injections or IV infusion • For individuals with ongoing exposure to SARS-CoV-2, repeat dosing of CAS 300 mg plus IMD	• Hypersensitivity, including anaphylaxis and infusion-related reactions • These AEs were observed over multiple trials where participants received CAS 600 mg plus IMD 600 mg or higher doses. • Injection site reactions, including ecchymosis and erythema, in clinical trial participants who received CAS plus IMD administered by SQ injections.	• Only for administration in health care settings by qualified health care providers who have immediate access to emergency medical services and medications that treat severe infusion reactions. • Monitor patient during the IV infusion or SQ injections and for at least 1 hour after the 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:** • CAS plus IMD is available through the FDA EUA as treatment for high-risk outpatients with mild to moderate COVID-19 and as PEP for certain high-risk individuals.[2] See Anti-SARS-CoV-2 Monoclonal Antibodies and Prevention of SARS-CoV-2 Infection for a list of high-risk conditions and criteria for use of CAS plus IMD. • A list of clinical trials is available: Casirivimab Plus Imdevimab

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				
300 mg by SQ injections or IV infusion every 4 weeks for duration of ongoing exposure.				
Sotrovimab (Anti-SARS-CoV-2 Monoclonal Antibody)				
Dose Recommended in EUA for Treatment of COVID-19: • SOT 500 mg administered by IV infusion over 30 minutes	• 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 that treat severe infusion reactions. • Monitor patient during the IV infusion and for at least 1 hour after the 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:** • SOT is available through the FDA EUA for the treatment of high-risk outpatients with mild to moderate COVID-19.[3] See Anti-SARS-CoV-2 Monoclonal Antibodies for a list of high-risk conditions. • A list of clinical trials is available: Sotrovimab
COVID-19 Convalescent Plasma				
Dose Recommended in 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[4] • 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 patient's vital signs at baseline and during and after transfusion.	• Drug products **should not be added** to the IV infusion line for the blood product.	• The decision to treat patients aged <18 years with COVID-19 CP should be based on an individualized assessment of risk and benefit.[5] • Patients with impaired cardiac function and heart failure may require a smaller volume of CP or a slower transfusion rate. **Availability:** • High-titer COVID-19 CP is available through the FDA EUA for hospitalized patients with COVID-19.[6] See Convalescent Plasma. • A list of clinical trials is available: COVID-19 Convalescent Plasma

Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
SARS-CoV-2-Specific Immunoglobulin				
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[4]	• Monitor for transfusion-related reactions. • Monitor patient's vital signs at baseline and during and after transfusion.	• Drug products **should not be added** to the IV infusion line for the blood product.	• A list of clinical trials is available: SARS-CoV-2 Immunoglobulin

Key: AE = adverse event; BAM = bamlanivimab; CAS = casirivimab; CP = convalescent plasma; CYP = cytochrome P450; ETE = etesevimab; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; IMD = imdevimab; IV = intravenous; the Panel = the COVID-19 Treatment Guidelines Panel; PEP = post-exposure prophylaxis; RBC = red blood cell; SOT = sotrovimab; SQ = subcutaneous; TACO = transfusion-associated circulatory overload; TRALI = transfusion-related acute lung injury

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

Last Updated: 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 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]

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: October 19, 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 (IL-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
- Colchicine for nonhospitalized patients
- Fluvoxamine
- Granulocyte-macrophage colony-stimulating factor inhibitors for hospitalized patients
- Inhaled budesonide
- Interferon beta for the treatment of early (i.e., <7 days from symptom onset) mild to moderate COVID-19

The Panel **recommends against** the use of the following immunomodulators for the treatment of COVID-19, except in a clinical trial:

- **Baricitinib** plus **tocilizumab (AIII)**
- **Canakinumab (BIIa)**
- **Colchicine** for hospitalized patients **(AI)**
- **Interferons (alfa or beta)** for the treatment of severely or critically ill patients with COVID-19 **(AIII)**
- **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)**

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

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

Colchicine

Last Updated: July 8, 2021

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 mechanisms that reduce the chemotaxis of neutrophils, inhibit inflammasome signaling, and decrease the production of cytokines such as interleukin-1 beta.[3] When colchicine is administered early in the course of COVID-19, these mechanisms may mitigate or prevent inflammation-associated manifestations of the disease. These anti-inflammatory properties (as well as the drug's limited immunosuppressive potential, widespread availability, and favorable safety profile) have prompted investigation of colchicine for the treatment of COVID-19.

Recommendations

- There is insufficient evidence for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of colchicine for the treatment of nonhospitalized patients with COVID-19.
- The Panel **recommends against** the use of colchicine for the treatment of hospitalized patients with COVID-19 **(AI)**.

Rationale

For Nonhospitalized Patients With COVID-19

A large randomized trial evaluating colchicine in outpatients with COVID-19 (COLCORONA) did not reach its primary efficacy endpoint of reducing hospitalizations and death. However, a slight reduction in hospitalizations was observed in the subset of patients whose diagnosis was confirmed by a positive SARS-CoV-2 polymerase chain reaction (PCR) result from a nasopharyngeal (NP) swab. Given that the trial did not reach its primary endpoint, only a very modest effect size was demonstrated in the subgroup of PCR-positive patients, and more gastrointestinal adverse events occurred in the colchicine arm than in the usual care arm, the Panel felt that additional evidence is needed to develop recommendations on using colchicine for the treatment of nonhospitalized patients with COVID-19.[4]

For Hospitalized Patients With COVID-19

In a randomized trial in hospitalized patients with COVID-19 (RECOVERY), colchicine demonstrated no benefit with regards to 28-day mortality or any secondary outcomes.[5] COLCORONA and RECOVERY are described more fully below.

Clinical Data for COVID-19

Colchicine in Nonhospitalized Patients With COVID-19: The COLCORONA Trial

COLCORONA was a contactless, double-blind, placebo-controlled randomized trial in outpatients who were diagnosed with COVID-19 within 24 hours of enrollment. Participants had to have at least one risk factor for COVID-19 complications, including age ≥70 years, body mass index ≥30, diabetes mellitus, uncontrolled hypertension, known respiratory disease, heart failure or coronary disease, fever ≥38.4°C within the last 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 colchicine 0.5 mg twice daily for 3 days and then once daily for 27 days or placebo. 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. Given the contactless design of the study, outcomes were ascertained by participant self-report via telephone at 15 and 30 days after randomization; in some cases, clinical data were confirmed by medical chart reviews.[4]

Results

- The study enrolled 4,488 participants.
- The primary endpoint occurred in 104 of 2,235 participants (4.7%) in the colchicine arm and 131 of 2,253 participants (5.8%) in the placebo arm (OR 0.79; 95% CI, 0.61–1.03; *P* = 0.08).
- There were no statistically significant differences in the secondary outcomes between the arms.
- In a prespecified analysis of 4,159 participants who had a SARS-CoV-2 diagnosis confirmed by PCR testing of an NP specimen (93% of those enrolled), those in the colchicine arm were less likely to reach the primary endpoint (96 of 2,075 participants [4.6%]) than those in the placebo arm (126 of 2,084 participants [6.0%]; OR 0.75; 95% CI, 0.57–0.99; *P* = 0.04). In this subgroup of patients with PCR-confirmed SARS-CoV-2 infection, there were fewer hospitalizations (a secondary outcome) in the colchicine arm (4.5% of patients) than in the placebo arm (5.9% of patients; OR 0.75; 95% CI, 0.57–0.99).
- More gastrointestinal adverse events occurred in the colchicine arm, including diarrhea (occurred in 13.7% of patients vs. in 7.3% of patients in the placebo arm; *P* < 0.0001). Unexpectedly, more pulmonary emboli were reported in the colchicine arm than in the placebo arm (11 events [0.5% of patients] vs. 2 events [0.1% of patients]; *P* = 0.01).

Limitations

- Due to logistical difficulties with staffing, the trial was stopped at approximately 75% of the target enrollment, which may have limited the study's power to detect differences for the primary outcome.
- There was uncertainty as to the accuracy of COVID-19 diagnoses in presumptive cases.
- Some patient-reported clinical outcomes were potentially misclassified.

Colchicine in Hospitalized Patients With COVID-19: The RECOVERY Trial

This study has not been peer reviewed.

RECOVERY randomized hospitalized patients with COVID-19 to receive colchicine (1 mg loading dose, followed by 0.5 mg 12 hours later, and then 0.5 mg twice daily for 9 days or until discharge) or usual care.[5]

Results

- The study enrolled 11,340 participants.
- At randomization, 10,603 patients (94%) were receiving corticosteroids.
- The primary endpoint of all-cause mortality at Day 28 occurred in 1,173 of 5,610 participants (21%) in the colchicine arm and 1,190 of 5,730 participants (21%) in the placebo arm (rate ratio 1.01; 95% CI, 0.93–1.10; *P* = 0.77).
- There were no statistically significant differences between the arms for the secondary outcomes of median time to being discharged alive, discharge from the hospital within 28 days, and receipt of invasive mechanical ventilation or death.
- The incidence of new cardiac arrhythmias, bleeding events, and thrombotic events was similar in the two arms. Two serious adverse events were attributed to colchicine: one case of severe acute kidney injury and one case of rhabdomyolysis.

Limitations

- The trial's open-label design may have introduced bias for assessing some of the secondary endpoints.

Study of the Effects of Colchicine in Hospitalized Patients With COVID-19: The GRECCO-19 Trial

GRECCO-19 was a small, prospective, open-label randomized clinical trial in 105 patients hospitalized with COVID-19 across 16 hospitals in Greece. Patients were assigned 1:1 to receive standard of care with colchicine (1.5 mg loading dose, followed by 0.5 mg after 60 minutes and then 0.5 mg twice daily until hospital discharge or for up to 3 weeks) or standard of care alone.[6]

Results

- Fewer patients in the colchicine arm (1 of 55 patients) than in the standard of care arm (7 of 50 patients) reached the primary clinical endpoint of deterioration in clinical status from baseline by two points on a seven-point clinical status scale (OR 0.11; 95% CI, 0.01–0.96).
- Participants in the colchicine group were significantly more likely to experience diarrhea (occurred in 45.5% vs. 18.0% of participants in the colchicine and standard of care arms, respectively; $P = 0.003$).

Limitations

- The overall sample size and the number of clinical events reported were small.
- The study design was open-label treatment assignment.

The results of several small randomized trials and retrospective cohort studies that have evaluated various doses and durations of colchicine in hospitalized patients with COVID-19 have been published in peer-reviewed journals or made available as preliminary, non-peer-reviewed reports.[7-10] Some have shown 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 have reported higher discharge rates or fewer deaths among patients who received colchicine than among those who received comparator drugs or placebo. However, the ability to interpret the findings of these studies is also constrained by significant design or methodological limitations, including small sample size, open-label designs, and differences in the clinical and demographic characteristics of participants and permitted use of various cotreatments (e.g., remdesivir, corticosteroids) 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. Use of colchicine should be avoided in patients with severe renal insufficiency, and patients with moderate renal insufficiency who receive the drug should be monitored for adverse effects. Caution should be used when colchicine is coadministered with drugs that inhibit cytochrome P450 (CYP) 3A4 and/or P-glycoprotein (P-gp) because such use may increase the risk of colchicine-induced adverse effects due to significant increases in colchicine plasma levels. 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 CYP3A4 and P-gp pathways.[11,12] 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.[11,13]

Considerations in Children

Colchicine use in children is limited to the treatment of periodic fever syndromes, primarily familial Mediterranean fever. There are no data on the use of colchicine to treat pediatric acute COVID-19 or multisystem inflammatory syndrome in children (MIS-C).

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Corticosteroids

Last Updated: October 19, 2021

Patients with severe COVID-19 can develop a systemic inflammatory response that can lead to lung injury and multisystem organ dysfunction. It has been proposed that the potent anti-inflammatory effects of corticosteroids might prevent or mitigate these deleterious effects.

Both beneficial and deleterious clinical outcomes have been reported with use of corticosteroids (mostly prednisone or methylprednisolone) in patients with pulmonary infections. In patients with *Pneumocystis jirovecii* pneumonia and hypoxemia, prednisone therapy reduced the risk of death.[1] However, during outbreaks of previous novel coronavirus infections (i.e., Middle East respiratory syndrome [MERS] and severe acute respiratory syndrome [SARS]), corticosteroid therapy was associated with delayed virus clearance.[2,3] In patients with severe pneumonia caused by influenza viruses, corticosteroid therapy appears to result in worse clinical outcomes, including secondary bacterial infections and death.[4]

Corticosteroid therapy has also been studied in critically ill patients with acute respiratory distress syndrome (ARDS) with conflicting results.[5-7] Use of corticosteroids in patients with ARDS was evaluated in seven randomized controlled trials that included a total of 851 patients.[6-12] A meta-analysis of these trial results demonstrated that, compared with placebo, corticosteroid therapy reduced the risk of all-cause mortality (risk ratio 0.75; 95% CI, 0.59–0.95) and the duration of mechanical ventilation (mean difference -4.93 days; 95% CI, -7.81 to -2.06 days).[13,14]

Corticosteroid use for the treatment of COVID-19 has been studied in clinical trials (see Tables 4a and 4b for more information). The COVID-19 Treatment Guidelines Panel's (the Panel) recommendations for the use of corticosteroids in patients with COVID-19 are based on the results from these studies.

Recommendations

For nonhospitalized patients 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 budesonide for the treatment of COVID-19.

For hospitalized patients 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.

Rationale

The Panel's recommendations on the use of corticosteroids for COVID-19 in nonhospitalized patients reflect a lack of data regarding their use in this population. In the RECOVERY trial (described below), dexamethasone was shown to reduce mortality in hospitalized patients with COVID-19 who required supplemental oxygen; however, treatment with dexamethasone was stopped at the time of hospital discharge. Because nonhospitalized patients were not included in the RECOVERY trial, the safety and efficacy of corticosteroid use for COVID-19 in this population have not been established. Moreover, 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 (see Therapeutic Management of Nonhospitalized Adults With COVID-19).

The Panel's recommendations on the use of corticosteroids for COVID-19 in hospitalized patients are largely based on data from the RECOVERY trial. This large, multicenter, open-label randomized controlled trial performed in the United Kingdom randomized 6,425 hospitalized patients to receive up to 10 days of dexamethasone plus the standard of care or the standard of care only. Mortality at Day 28 was lower among the patients who received dexamethasone than among those who received the standard of care alone.[15] This mortality benefit was observed in patients who were mechanically ventilated or required supplemental oxygen at enrollment. No benefit of dexamethasone was seen in patients who did not require supplemental oxygen at enrollment. Details of the RECOVERY trial are summarized in Table 4d.[15]

Systemic corticosteroids used in combination with other agents including antivirals and immunomodulators, such as tocilizumab (see Interleukin-6 Inhibitors)[16,17] or baricitinib (see Kinase Inhibitors),[18] have demonstrated clinical benefit in subsets of hospitalized patients with COVID-19.

Various formulations of systemic corticosteroids used in different doses for varying durations have been studied in patients with COVID-19 in several smaller randomized controlled trials.[19-23] Some of these trials were stopped early due to under-enrollment following the release of the results from the RECOVERY trial. Consequently, the sample size of many these trials was insufficient to assess efficacy, and therefore evidence to support the use of methylprednisolone and hydrocortisone for the treatment of COVID-19 is not as strong as that demonstrated for dexamethasone in the RECOVERY trial.

Please see Tables 4a and 4b for data from clinical trials that have evaluated corticosteroid use for the treatment of COVID-19.

Systemic Corticosteroids Other Than Dexamethasone

- 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 (oral or intravenous [IV])[24] are:
  - Prednisone 40 mg
  - Methylprednisolone 32 mg
  - Hydrocortisone 160 mg
- Half-life, duration of action, and frequency of administration vary among corticosteroids.
  - *Long-acting corticosteroid:* Dexamethasone; half-life 36 to 72 hours, administer once daily.
  - *Intermediate-acting corticosteroids:* Prednisone and methylprednisolone; half-life 12 to 36 hours, administer once daily or in two divided doses daily.
  - *Short-acting corticosteroid:* Hydrocortisone; half-life 8 to 12 hours, administer in two to four divided doses daily.
- Hydrocortisone is commonly used to manage septic shock in patients with COVID-19; see Hemodynamics for more information. Unlike other corticosteroids previously studied in patients with ARDS, dexamethasone lacks mineralocorticoid activity and thus has minimal effect on sodium balance and fluid volume.[9]

Inhaled Corticosteroids

Budesonide is a synthetic, inhaled corticosteroid with potent glucocorticoid activity and weak mineralocorticoid activity. It has broad anti-inflammatory properties and has Food and Drug Administration-labeled indications for the management of chronic respiratory diseases including asthma and chronic obstructive pulmonary disease. Certain inhaled corticosteroids have been shown to impair viral replication of SARS-CoV-2[25] and downregulate expression of the receptors used for cell entry.[26,27] These mechanisms support the potential of inhaled corticosteroids as therapeutic agents for COVID-19. However, observational studies have found that long-term use of inhaled corticosteroids prescribed for non-COVID-19 respiratory diseases either had no effect on COVID-19 outcomes or increased the risk of hospitalization.[28,29] More recently, two open-label randomized controlled trials provided additional insights regarding the role of inhaled budesonide 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 budesonide for the treatment of COVID-19.

Rationale

Inhaled budesonide was studied in two open-label randomized controlled trials in outpatients with mild symptoms of COVID-19.[30,31] The small STOIC trial suggested that in adult outpatients with mild COVID-19, initiation of inhaled budesonide may reduce the need for urgent care or emergency department assessment or hospitalization.[30] PRINCIPLE, a larger open-label trial in nonhospitalized patients with COVID-19 at high risk of disease progression, found that inhaled budesonide did not affect the rate of hospitalization or death but did reduce time to self-reported recovery.[31] The findings from these trials should be interpreted with caution given the open-label design of the studies and other limitations as outlined in the study description in Table 4b. Additional trials of inhaled corticosteroids are ongoing.

Most of the patients included in the PRINCIPLE trial would also have been candidates for anti-SARS-CoV-2 monoclonal antibody (mAb) therapy, which has been shown to reduce the risk of hospitalization and death in patients who have mild to moderate COVID-19 and certain risk factors for disease progression. Whether inhaled budesonide provides any additional benefit for patients who have received anti-SARS-CoV-2 mAb therapy is unknown.

Monitoring, Adverse Effects, and Drug-Drug Interactions for Systemic Corticosteroids

- Clinicians should closely monitor patients with COVID-19 who are receiving dexamethasone for adverse effects (e.g., hyperglycemia, secondary infections, psychiatric effects, avascular necrosis).
- 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, herpesvirus infections, strongyloidiasis, tuberculosis).[32-36]
- Cases of severe and disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with tocilizumab and corticosteroids.[37,38] Many clinicians would initiate empiric treatment for strongyloidiasis (e.g., with ivermectin) with or without serologic testing in patients from areas where *Stronglyloides* is endemic (i.e., tropical, subtropical, or warm temperate areas).[39]
- Combining systemic corticosteroids with other immunosuppressants, such as tocilizumab or baricitinib, could theoretically increase the risk of secondary infections. However, this adverse

effect has not been reported in clinical trials to date.

- Dexamethasone is a moderate cytochrome P450 (CYP) 3A4 inducer. As such, it may reduce the concentration and potential efficacy of concomitant medications that are CYP3A4 substrates. Clinicians should review a patient's medication regimen to assess potential interactions.
- Dexamethasone should be continued for up to 10 days or until hospital discharge, whichever comes first (see Therapeutic Management of Hospitalized Adults With COVID-19).

Considerations in Pregnancy

A short course of betamethasone or dexamethasone, which are known to cross the placenta, is routinely used to decrease neonatal complications of prematurity in women with threatened preterm delivery.[40,41]

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

Considerations in Children

The safety and effectiveness of dexamethasone or other corticosteroids for COVID-19 treatment have not been sufficiently evaluated in pediatric patients and caution is warranted when extrapolating recommendations for adults to patients aged <18 years. The Panel recommends using **dexamethasone** for children with COVID-19 who require high-flow oxygen, noninvasive ventilation, invasive 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). 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 on a case-by-case basis. 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. Corticosteroid use has been described in the treatment of multisystem inflammatory syndrome in children (MIS-C) in multiple case series. It is the second most used therapy after IV immunoglobulin for MIS-C.[42,43] Please refer to Special Considerations in Children for more information on the management of MIS-C.

Clinical Trials

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

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Table 4a. Systemic Corticosteroids: Selected Clinical Data

Last Updated: August 4, 2021

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.

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

Study Design	Methods	Results	Limitations and Interpretation
RECOVERY Trial: Dexamethasone in Hospitalized Patients With COVID-19—Preliminary Report[1], continued			
		• The treatment effect of dexamethasone varied by baseline severity of COVID-19. Survival benefit appeared greatest among participants who required IMV at randomization. Among these participants, 28-day mortality was 29.3% in dexamethasone arm vs. 41.4% in SOC arm (rate ratio 0.64; 95% CI, 0.51–0.81). • Among patients who required supplemental oxygen but not mechanical ventilation at randomization, 28-day mortality was 23.3% in dexamethasone arm vs. 26.2% in SOC arm (rate ratio 0.82; 95% CI, 0.72–0.94). • No survival benefit in participants who did not require oxygen therapy at enrollment. Among these participants, 28-day mortality was 17.8% in dexamethasone arm vs. 14.0% in SOC arm (rate ratio 1.19; 95% CI, 0.91–1.55).	• It is unclear whether younger patients were more likely to receive mechanical ventilation than patients aged >80 years, given similar disease severity at baseline, with older patients preferentially assigned to oxygen therapy. • The high baseline mortality of this patient population may limit generalizability of the study results to populations with a lower baseline mortality. **Interpretation:** • In hospitalized patients with severe COVID-19 who required oxygen support, using dexamethasone 6 mg daily for up to 10 days reduced mortality at 28 days, with the greatest benefit seen in those who were mechanically ventilated at baseline. • There was no observed survival benefit of dexamethasone in patients who did not require oxygen support at baseline.
Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19[2]			
Meta-analysis of 7 RCTs of corticosteroids in critically ill patients with COVID-19 in multiple countries (n = 1,703)	**Key Inclusion Criteria:** • RCTs evaluating corticosteroids in critically ill patients with COVID-19 (identified via comprehensive search of ClinicalTrials.gov, Chinese Clinical Trial Registry, and EU Clinical Trials Register) **Interventions:** • Corticosteroids (i.e., dexamethasone, hydrocortisone, methylprednisolone) • Usual care or placebo	**Number of Participants:** • Corticosteroids (n = 678) and usual care or placebo (n = 1,025) **Participant Characteristics:** • Median age was 60 years. • 29% of patients were women. • 1,559 patients (91.5%) were on mechanical ventilation. • 47% of patients were on vasoactive agents at randomization across the 6 trials that reported this information.	**Key Limitations:** • The design of the trials included in the meta-analysis differed in several ways, including the following: • Definition of critical illness • Specific corticosteroid used • Dose of corticosteroid • Duration of corticosteroid treatment • Type of control group (i.e., usual care or placebo) • Reporting of SAEs

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

Study Design	Methods	Results	Limitations and Interpretation
Metcovid: Methylprednisolone as Adjunctive Therapy for Patients Hospitalized With COVID-19[3]			
Double-blind, Phase 2b, RCT of short-course methylprednisolone in hospitalized patients with confirmed or suspected COVID-19 pneumonia in a single center in Brazil (n = 416)	**Key Inclusion Criteria:** • Aged ≥18 years • Suspected or confirmed COVID-19 • SpO_2 ≤94% in room air *or* while using supplementary oxygen *or* under IMV **Key Exclusion Criteria:** • Hypersensitivity to methylprednisolone • Chronic use of corticosteroids or immunosuppressive agents • HIV, decompensated cirrhosis, chronic renal failure **Interventions:** • Methylprednisolone IV 0.5 mg/kg twice daily for 5 days • Placebo (saline) IV **Primary Endpoint:** • Mortality by Day 28 **Secondary Endpoints:** • Early mortality at Days 7 and 14 • Need for mechanical ventilation by Day 7 • Need for insulin by Day 28 • Positive blood culture at Day 7, sepsis by Day 28 • Mortality by Day 28 in specified subgroups	**Number of Participants:** • mITT analysis (n = 393): Methylprednisolone (n = 194) and placebo (n = 199) **Participant Characteristics:** • Mean age was 55 years. • 65% of patients were men. • 29% of patients had diabetes. • At enrollment, 34% of participants in each group required IMV; 51% in methylprednisolone group and 45% in placebo group required supplemental oxygen. • Median time from illness onset to randomization was 13 days (IQR 9–16). • None of the participants received anti-IL-6, anti-IL-1, RDV, or convalescent plasma. • Hydrocortisone use for shock among patients was 8.7% in methylprednisolone group and 7.0% in placebo group. **Primary Outcomes:** • No difference in 28-day mortality: 37.1% in methylprednisolone arm vs. 38.2% in placebo arm (HR 0.92; 95% CI, 0.67–1.28; *P* = 0.63). **Secondary Outcomes:** • No difference between groups in early mortality at Day 7 (HR 0.68; 95% CI, 0.43–1.06) or Day 14 (HR 0.82; 95% CI, 0.57–1.18). • No difference in need for mechanical ventilation by Day 7: 19.4% of methylprednisolone recipients vs. 16.8% of placebo recipients (*P* = 0.65).	**Key Limitations:** • The median days from illness onset to randomization was longer than in other corticosteroid studies. • The high baseline mortality of this patient population may limit generalizability of the study results to populations with a lower baseline mortality. **Interpretation:** • Use of weight-based methylprednisolone for 5 days did not reduce overall 28-day mortality. • In a post hoc subgroup analysis, mortality among those aged >60 years was lower in the methylprednisolone group than in the placebo group.

Study Design	Methods	Results	Limitations and Interpretation
Metcovid: Methylprednisolone as Adjunctive Therapy for Patients Hospitalized With COVID-19[3], continued			
		• No significant difference between the methylprednisolone and placebo groups in need for insulin (59.5% vs. 49.4% of patients), positive blood cultures at Day 7 (8.3% vs. 8.0% of patients), or sepsis by Day 28 (38.1% vs. 38.7% of patients). • In post hoc analysis, 28-day mortality in participants aged >60 years was lower in methylprednisolone group than in placebo group (46.6% vs. 61.9%; HR 0.63; 95% CI, 0.41–0.98).	
CoDEX: Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19[4]			
Multicenter RCT in patients with COVID-19 and moderate to severe ARDS in Brazil (n = 299)	**Key Inclusion Criteria:** • Aged ≥18 years • Confirmed or suspected COVID-19 • On mechanical ventilation within 48 hours of meeting criteria for moderate to severe ARDS with PaO_2/FiO_2 ≤200 mm Hg **Key Exclusion Criteria:** • Recent corticosteroid use • Use of immunosuppressive drugs in the past 21 days • Expected death in next 24 hours **Interventions:** • Dexamethasone 20 mg IV daily for 5 days, then 10 mg IV daily for 5 days or until ICU discharge plus SOC • SOC alone **Primary Endpoint:** • Mean number of days alive and free from mechanical ventilation by Day 28	**Number of Participants:** • ITT analysis (n = 299): Dexamethasone plus SOC (n = 151) and SOC alone (n = 148) **Participant Characteristics:** • Dexamethasone group included more women than the SOC group (40% vs. 35%), more patients with obesity (31% vs. 24%), and fewer patients with diabetes (38% vs. 47%). • Other baseline characteristics were similar for the dexamethasone and SOC groups: • Mean age of 60 vs. 63 years; vasopressor use by 66% vs. 68% of patients; mean PaO_2/FiO_2 of 131 mm Hg vs. 133 mm Hg. • Median time from symptom onset to randomization was 9–10 days. • Median time from mechanical ventilation to randomization was 1 day. • No patients received RDV; anti-IL-6 and convalescent plasma were not widely available. • Median duration of dexamethasone therapy was 10 days (IQR 6–10 days). • 35% of patients in SOC alone group also received corticosteroids.	**Key Limitations:** • Open-label study • The study was underpowered to assess some outcomes because it stopped enrollment after data from the RECOVERY trial were released. • During the study, 35% of the patients in the SOC group received corticosteroids for shock, bronchospasm, or other reasons. • Patients who were discharged from the hospital before 28 days were not followed for rehospitalization or mortality. • The high baseline mortality of the patient population may limit generalizability of the study results to populations with a lower baseline mortality.

Study Design	Methods	Results	Limitations and Interpretation
CoDEX: Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19[4], continued			
	Secondary Endpoints: • All-cause mortality at Day 28 • ICU-free days by Day 28 • Duration of mechanical ventilation by Day 28 • Score on 6-point WHO ordinal scale at Day 15 • SOFA score at 7 days • Components of the primary outcome or in the outcome of discharged alive within 28 days	**Primary Outcomes:** • The mean number of days alive and free from mechanical ventilation by Day 28 was higher in the dexamethasone group than in the SOC group (6.6 vs. 4.0 days, estimated difference of 2.3 days; 95% CI, 0.2–4.4; *P* = 0.04). **Secondary Outcomes:** • There were no differences between the dexamethasone and SOC groups for the following outcomes: • All-cause mortality at Day 28 (56.3% vs. 61.5%: HR 0.97; 95% CI, 0.72–1.31; *P* = 0.85). • ICU-free days by Day 28 (mean of 2.1 vs. 2.0 days; *P* = 0.50). • Duration of mechanical ventilation by Day 28 (mean of 12.5 vs.13.9 days; *P* = 0.11). • Score on 6-point WHO ordinal scale at Day 15 (median score of 5 for both groups). • The mean SOFA score at 7 days was lower in the dexamethasone group than in the SOC group (6.1 vs. 7.5, difference -1.16; 95% CI, -1.94 to -0.38; *P* = 0.004). • The following safety outcomes were comparable for dexamethasone and SOC groups: need for insulin (31.1% vs. 28.4%), new infections (21.9% vs. 29.1%), bacteremia (7.9% vs. 9.5%), and other SAEs (3.3% vs. 6.1%). • In post hoc analysis, the dexamethasone group had a lower cumulative probability of death or mechanical ventilation at Day 15 than the SOC group (67.5% vs. 80.4%; OR 0.46; 95% CI, 0.26–0.81; *P* = 0.01).	**Interpretation:** • Compared with SOC alone, dexamethasone at a higher dose than used in the RECOVERY trial plus SOC increased the number of days alive and free of mechanical ventilation over 28 days of follow-up in patients with COVID-19 and moderate to severe ARDS. • Dexamethasone was not associated with an increased risk of AEs in this population. • More than one-third of those randomized to the standard care alone group also received corticosteroids; it is impossible to determine the effect of corticosteroid use in these patients on the overall study outcomes.

Study Design	Methods	Results	Limitations and Interpretation
Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19[5]			
Multicenter, double-blind, sequential RCT in patients with confirmed or suspected COVID-19 and acute respiratory failure in France (n = 149)	**Key Inclusion Criteria:** • Aged ≥18 years • Confirmed SARS-CoV-2 infection or radiographically suspected COVID-19, with at least 1 of 4 severity criteria: • Need for mechanical ventilation with PEEP ≥5 cm H_2O • High-flow oxygen with PaO_2/FiO_2 <300 mm Hg and FiO_2 ≥50% • Reservoir mask oxygen with PaO_2/FiO_2 <300 mm Hg (estimated) • Pneumonia severity index >130 (scoring table) **Key Exclusion Criteria:** • Septic shock • Do-not-intubate orders **Interventions:** • Continuous infusion hydrocortisone 200 mg/day until Day 7, then hydrocortisone 100 mg/day for 4 days, and then hydrocortisone 50 mg/day for 3 days, for a total treatment duration of 14 days • Patients who showed clinical improvement by Day 4 were switched to a shorter 8-day regimen **Primary Endpoint:** • Treatment failure (defined as death or persistent dependency on mechanical ventilation or high-flow oxygen) by Day 21	**Number of Participants:** • ITT analysis (n = 149 participants): Hydrocortisone (n = 76) and placebo (n = 73) **Participant Characteristics:** • Mean age of participants was 62 years; 70% were men; median BMI was 28. • 96% of participants had confirmed SARS-CoV-2 infection. • Median symptom duration before randomization was 9 days in hydrocortisone group vs. 10 days in placebo group. • 81% of the patients overall were mechanically ventilated, and 24% in hydrocortisone group and 18% in placebo group were receiving vasopressors. • Among the patients receiving concomitant COVID-19 treatment, 3% received RDV, 14% LPV/RTV, 13% HCQ, and 34% HCQ plus AZM. • Median treatment duration was 10.5 days in hydrocortisone group vs. 12.8 days in placebo group (*P* = 0.25). **Primary Outcome:** • No difference in the proportion of patients with treatment failure by Day 21, which occurred in 32 of 76 patients (42.1%) in hydrocortisone group and 37 of 73 patients (50.7%) in placebo group (difference -8.6%; 95% CI, -24.9% to 7.7%; *P* = 0.29). **Secondary Outcomes:** • No difference in the need for intubation, rescue strategies, or oxygenation (i.e., change in PaO_2/FiO_2). • Among the patients who did not require mechanical ventilation at baseline, 8 of 16 patients (50%) in hydrocortisone group required subsequent intubation vs. 12 of 16 (75%) in placebo group.	**Key Limitations:** • Small sample size. Planned sample size of 290, but 149 enrolled because study was terminated early after the release of results from the RECOVERY trial. • Limited information about comorbidities (e.g., hypertension) • Participants' race and/or ethnicity were not reported. • Nosocomial infections were recorded but not adjudicated. **Interpretation:** • Compared to placebo, hydrocortisone did not reduce treatment failure (defined as death or persistent respiratory support) at Day 21 in ICU patients with COVID-19 and acute respiratory failure. • Because this study was terminated early, it is difficult to make conclusions about the efficacy and safety of hydrocortisone therapy. • The starting dose of hydrocortisone used in this study were slightly higher than the 6 mg dose of dexamethasone used in the RECOVERY study. The hydrocortisone dose was adjusted according to clinical response.

Study Design	Methods	Results	Limitations and Interpretation
Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19[5], continued			
	Secondary Endpoints: • Need for intubation, rescue strategies, or oxygenation (i.e., change in PaO_2/FiO_2) • Nosocomial infections on Day 28 • Clinical status on Day 21	• 3 SAEs were reported (cerebral vasculitis, cardiac arrest due to PE, and intra-abdominal hemorrhage from anticoagulation for PE); all occurred in the hydrocortisone group, but none were attributed to the intervention. • No difference between the groups in proportion of patients with nosocomial infections on Day 28. • In post hoc analysis, clinical status on Day 21 did not significantly differ between the groups except for fewer deaths in the hydrocortisone group (14.7% of patients died vs. 27.4% in placebo group; $P = 0.06$): • By Day 21, 57.3% of patients in hydrocortisone group vs. 43.8% in placebo group were discharged from the ICU and 22.7% in hydrocortisone group vs. 23.3% in placebo group were still mechanically ventilated.	
REMAP-CAP COVID-19 Corticosteroid Domain (CAPE COD): Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19[6]			
Randomized, embedded, multifactorial, adaptive platform trial of patients with severe COVID-19 in multiple countries (n = 403)	**Key Inclusion Criteria:** • Aged ≥18 years • Presumed or confirmed SARS-CoV-2 infection • ICU admission for respiratory or cardiovascular organ support **Key Exclusion Criteria:** • Presumed imminent death • Systemic corticosteroid use • >36 hours since ICU admission **Interventions:** • Hydrocortisone 50 mg 4 times daily for 7 days	**Number of Participants:** • mITT analysis (n = 384): Fixed-dose hydrocortisone (n = 137), shock-based hydrocortisone (n = 146), and no hydrocortisone (n = 101) **Participant Characteristics:** • Mean age was 60 years. • 71% of patients were men. • Mean BMI was 29.7–30.9. • 50% to 64% of patients received mechanical ventilation. **Primary Outcome:** • No difference in organ-support free-days at Day 21 (median of 0 days in each group).	**Key Limitations:** • Early termination following release of RECOVERY study results • Randomized study, but open label **Interpretation:** • Corticosteroids did not significantly increase support-free days in either the fixed-dose hydrocortisone or the shock-dependent hydrocortisone group, although the early termination of the trial led to limited power to detect difference between the study arms.

Study Design	Methods	Results	Limitations and Interpretation
REMAP-CAP COVID-19 Corticosteroid Domain (CAPE COD): Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19[6], continued			
	• Septic shock-based hydrocortisone 50 mg 4 times daily for the duration of shock • No hydrocortisone **Primary Endpoint:** • Days free of respiratory and cardiovascular organ support up to Day 21 (for this ordinal outcome, patients who died were assigned -1 day) **Secondary Endpoints:** • In-hospital mortality • SAEs	• Compared to the no hydrocortisone group, median adjusted OR for the primary outcome: • OR 1.43 (95% CrI, 0.91–2.27) with 93% Bayesian probability of superiority for the fixed-dose hydrocortisone group. • OR 1.22 (95% CrI, 0.76–1.94) with 80% Bayesian probability of superiority for the shock-based hydrocortisone group. **Secondary Outcomes:** • No difference between the groups in mortality; 30%, 26%, and 33% of patients died in the fixed-dose, shock-based, and no hydrocortisone groups, respectively. • SAEs reported in 3%, 3%, and 1% of patients in the fixed-dose, shock-based, and no hydrocortisone groups, respectively.	
Efficacy of Early, Low-Dose, Short-Term Corticosteroids in Adults Hospitalized with Nonsevere COVID-19 Pneumonia[7]			
Retrospective cohort study in patients with nonsevere COVID-19 pneumonia and propensity score-matched controls in China (n = 55 matched case-control pairs)	**Key Inclusion Criteria:** • Aged ≥16 years • Confirmed COVID-19 • Pneumonia on chest CT scan **Key Exclusion Criteria:** • Severe pneumonia defined as having any of the following: respiratory distress, respiratory rates >30 breaths/min, SpO_2 <93%, oxygenation index <300 mm Hg, mechanical ventilation, or shock	**Number of Participants:** • Corticosteroids (n = 55): IV methylprednisolone (n = 50) and prednisone (n = 5) • No corticosteroids (n = 55 matched controls chosen from 420 patients who did not receive corticosteroids) **Participant Characteristics:** • Median age was 58–59 years. • Median SpO_2 was 95%. • 42% of patients in corticosteroids group and 46% in no corticosteroids group had comorbidities, 35% to 36% had HTN, and 11% to 13% had diabetes.	**Key Limitations:** • Retrospective, case-control study. • Small sample size (55 case-control pairs). • Corticosteroid therapy was selected preferentially for patients who had more risk factors for severe progression of COVID-19; the propensity score matching may not have adjusted for some of the unmeasured confounders. • Selection bias in favor of the no corticosteroids group may have been introduced by excluding patients who used corticosteroids after progression to severe disease from the study.

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

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

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Table 4b. Inhaled Corticosteroids: Selected Clinical Data

Last Updated: October 19, 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 • Use of inhaled budesonide contraindicated **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 of 6 days from symptom onset to randomization **Primary Outcomes:** • COVID-19-related hospitalization or death 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 days to reported recovery: 11.8 in budesonide arm vs. 14.7 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 self-report **Interpretation:** • Inhaled budesonide reduced time to reported recovery but not COVID-related hospitalization or death. • The clinical significance of self-reported time to recovery in an open-label study is unclear.

Methods	Results	Limitations and Interpretation
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) • Usual care (n = 73) **Primary Endpoint:** • COVID-19-related urgent care visit, including ED visit or hospitalization	**Participant Characteristics:** • Mean age 45 years; 58% women • 9% with CVD; 5% with diabetes • 95% with positive SARS-CoV-2 RT-PCR result • Median of 3 days from symptom onset to randomization **Primary Outcomes:** • Median days of budesonide use: 7. • COVID-19-related urgent care visits or hospitalizations: 1% in budesonide arm vs.14% in usual care arm (relative risk reduction 91%).	**Key Limitations:** • Small, open label trial • Early termination after statistical analysis determined that additional participants would not alter outcome **Interpretation:** • In adult outpatients with mild COVID-19, inhaled budesonide may reduce the need for urgent care or ED assessment and/or hospitalization.

Key: CVD = cardiovascular disease; ED = emergency department; the Panel = the COVID-19 Treatment Guidelines Panel; PCR = polymerase chain reaction; RCT = randomized controlled trial; RT-PCR = reverse transcription polymerase chain reaction

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Fluvoxamine

Last Updated: April 23, 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 in 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] Further studies are needed to establish whether the anti-inflammatory effects of fluvoxamine observed in nonclinical studies also occur in humans beings and are clinically relevant in the setting of COVID-19.

Recommendation

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

Clinical Trial Data

Placebo-Controlled Randomized Trial in Nonhospitalized Adults With Mild COVID-19

In this contactless, double-blind, placebo-controlled randomized trial, nonhospitalized adults with mild COVID-19 confirmed by SARS-CoV-2 polymerase chain reaction (PCR) assay within 7 days of symptom onset were randomized to receive fluvoxamine up to 100 mg three times daily or matching placebo for 15 days. The primary endpoint was clinical deterioration (defined as having dyspnea or hospitalization for dyspnea or pneumonia and oxygen saturation [SpO_2] <92% on room air or requiring supplemental oxygen to attain SpO_2 ≥92%) within 15 days of randomization. Participants self-assessed their blood pressure, temperature, oxygen saturation, and COVID-19 symptoms and reported the information by email twice daily.[3]

Participant Characteristics

- A total of 152 participants were randomized to receive fluvoxamine (n = 80) or placebo (n = 72).
- The mean age of the participants was 46 years; 72% were women, 25% were Black, and 56% had obesity.

Results

- None of 80 participants (0%) who received fluvoxamine and six of 72 participants (8.3%) who received placebo reached the primary endpoint (absolute difference 8.7%; 95% CI, 1.8% to 16.5%; $P = 0.009$).
- Five participants in the placebo arm and one in the fluvoxamine arm required hospitalization.
- Only 76% of the participants completed the study, and 20% of the participants stopped responding to the electronic survey during the study period but were included in the final analysis.

Limitations

- The study had a small sample size.

- A limited number of events occurred.
- Ascertaining clinical deterioration was challenging because all assessments were done remotely.

Interpretation

In this small placebo-controlled trial, none of the participants who received fluvoxamine and six (8.3%) of those who received placebo reached the primary endpoint. However, due to the study's reliance on participant self-reports and missing data, it is difficult to draw definitive conclusions about the efficacy of fluvoxamine for the treatment of COVID-19.[3]

Prospective Observational Study During an Outbreak of SARS-CoV-2 Infections

A prospective, nonrandomized observational cohort study evaluated fluvoxamine for the treatment of COVID-19 in 113 outpatients who tested positive for SARS-CoV-2 antigen with the result confirmed by a PCR test. The trial was conducted in an occupational setting during an outbreak of COVID-19. Patients were offered the option of receiving fluvoxamine 50 mg twice daily for 14 days or no therapy.[4]

Patient Characteristics

- Of the 113 participants with positive SARS-CoV-2 antigen, 65 opted to take fluvoxamine and 48 did not.
- More of the patients who did not take fluvoxamine had hypertension. In addition, more of those who were Latinx and more of those who were initially symptomatic opted to take fluvoxamine.

Results

- At Day 14, none of the patients who received fluvoxamine versus 60% of those who did not had persistent symptoms (e.g., anxiety, difficulty concentrating, fatigue) ($P < 0.001$).
- By Day 14, none of the fluvoxamine-treated patients were hospitalized; six patients who did not receive fluvoxamine were hospitalized, including two patients who required care in the intensive care unit.
- No serious adverse events were reported following receipt of fluvoxamine.

Limitations

- The study was a nonrandomized trial.
- The study had a small sample size.
- Limited data were collected during the study.

Limitations (e.g., small sample size) and differences in study populations and fluvoxamine doses make it difficult to interpret and generalize the findings of these trials.

Additional studies, including a Phase 3 randomized controlled trial (ClinicalTrials.gov Identifier NCT04668950), are ongoing to provide more specific evidence-based guidance on the role of fluvoxamine for the treatment of COVID-19.

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), dermatologic reactions (sweating), and rarely suicidal ideation.

Fluvoxamine is a cytochrome P450 (CYP) D6 substrate and a potent inhibitor of CYP1A2 and 2C19 and a moderate inhibitor of CYP2C9, 2D6, and 3A4.[5] Fluvoxamine may enhance the anticoagulant effects of antiplatelets and anticoagulants. In addition, it can enhance the serotonergic effects of other SSRIs or monoamine oxidase inhibitors (MAOIs) resulting in serotonin syndrome. Fluvoxamine **should not be used** within 2 weeks of receipt of other SSRIs or MAOIs and should be used with caution with other QT-interval prolonging medications.

Considerations in Pregnancy

Fluvoxamine is not thought to increase the risk of congenital abnormalities; however, the data on its use in pregnancy are limited.[6,7] A small, increased risk of primary persistent pulmonary hypertension in the newborn associated with SSRI use in the late third trimester has not been excluded, although the absolute risk is likely low.[8] 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.[9] 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.[10] There are no data on the use of fluvoxamine for the prevention or treatment of COVID-19 in children.

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Granulocyte-Macrophage Colony-Stimulating Factor Inhibitors

Last Updated: July 8, 2021

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a myelopoietic growth factor and proinflammatory cytokine that plays a central role in a broad range of immune-mediated diseases. GM-CSF, 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 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. Preliminary data from a double-blind, placebo-controlled randomized 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. 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.[11-13] 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 invasive mechanical ventilation. Each of these GM-CSF inhibitors remains under investigation.

Clinical Data for COVID-19

Lenzilumab, mavrilimumab, and otilimab have been evaluated in clinical trials in hospitalized adults with SARS-CoV-2 pneumonia.[11-13] Clinical data are not yet available for gimsilumab or namilumab. The Panel's recommendations are based on the results of the available clinical studies. Clinical data on the use of anti-GM-CSF monoclonal antibodies for the treatment of COVID-19 are summarized in Table 4c.

Clinical Trials

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

Adverse Effects

The primary risks associated with GM-CSF inhibitors being reported and evaluated are related to bacterial infection. Other adverse events that have been reported with these agents include acute kidney injury and elevated liver transaminases.[10] Autoimmune pulmonary alveolar proteinosis has been associated with a high-titer of anti-GM-CSF auto-antibodies.[14]

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 4c. Granulocyte-Macrophage Colony-Stimulating Factor Inhibitors: Selected Clinical Data

Last Updated: July 8, 2021

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.

Study Design	Methods	Results	Limitations and Interpretation
Otilimab in Severe COVID-19 Pneumonia (OSCAR Trial)[1]			
Phase 2, double-blind RCT in patients with severe COVID-19 pulmonary disease in 17 countries, including the United States (n = 806) *This is a preliminary report that has not yet been peer reviewed.*	**Key Inclusion Criteria:** • Hospitalized adults with confirmed SARS-CoV-2 pneumonia • New onset of oxygenation impairment requiring high-flow oxygen (≥15 L/min), noninvasive ventilation, or IMV ≤48 hours before dosing • CRP or ferritin >ULN **Key Exclusion Criteria:** • Death considered likely within 48 hours • Multiple organ failure • SOFA score >10 if in the ICU • ECMO • Dialysis • High-dose noradrenaline (>0.15 ug/kg/min) or equivalent • More than 1 vasopressor **Interventions** *1:1 Randomization:* • Otilimab 90 mg IV as a single infusion • Placebo	**Number of Participants:** • mITT analysis (n = 793): otilimab (n = 395) and placebo (n = 398) • Participants were enrolled from May 28–November 15, 2020, across 108 study sites. **Participant Characteristics:** • Mean age was 59 years. • 77% received high-flow oxygen or noninvasive ventilation. • 22% were on IMV. • 52% were in the ICU but not on IMV. • 83% received corticosteroids; 34% received RDV • Participants were stratified by clinical status (ordinal scale 5 or 6) and age (<60 years, 60–69 years, and ≥70 years). **Primary Outcome:** • 277 of 389 participants (71%) in the otilimab arm vs. 262 of 393 participants (67%) in the placebo arm were alive and free of respiratory failure at Day 28 (model-adjusted absolute difference of 5.3%; 95% CI, -0.8 to 11.4; *P* = 0.09) **Key Secondary Outcomes:** • No difference in all-cause mortality at Day 60 between the otilimab arm and the placebo arm (23% vs. 24%; model-adjusted difference -2.4%; 95% CI, -8.0 to 3.3; *P* = 0.41)	**Key Limitations:** • Changes in SOC occurred during the study period and may have affected outcomes. • A preplanned subgroup analysis suggested a benefit of otilimab in participants aged ≥70 years, but subgroup analyses were not adjusted for multiple comparisons. **Interpretation:** • In this large study, no differences in outcomes were observed between the otilimab or placebo recipients with severe COVID-19 pneumonia, except for those in a subgroup of participants aged ≥70 years.

Study Design	Methods	Results	Limitations and Interpretation
Otilimab in Severe COVID-19 Pneumonia (OSCAR Trial)[1], continued			
	Primary Endpoint: • Proportion of participants alive and free of respiratory failure at Day 28 **Key Secondary Endpoints:** • All-cause mortality at Day 60 and time to all-cause mortality • Time to recovery • Admission to ICU • Time to ICU discharge	• No difference between the arms for other secondary endpoints • In a preplanned analysis, a benefit of otilimab was observed among those aged ≥70 years (n = 180): • 65.1% of otilimab recipients vs. 45.9% of placebo recipients met the primary endpoint (model-adjusted difference 19.1%; 95% CI, 5.2–33.1; *P* = 0.009) • Mortality at Day 60 was lower in otilimab arm than in placebo arm (27% vs. 41%; model-adjusted difference of 14.4%; 95% CI, 0.9–27.9; *P* = 0.04).	
Lenzilumab in Hospitalized Patients With COVID-19 Pneumonia (LIVE-AIR Trial)[2]			
Phase 3, double-blind RCT in hospitalized patients with severe COVID-19 pneumonia in the United States and Brazil (n = 520 across 29 study sites) *This is a preliminary report that has not yet been peer reviewed.*	**Key Inclusion Criteria:** • Hospitalized adults with confirmed SARS-CoV-2 pneumonia • SpO_2 ≤94% on room air or requiring low-flow supplemental oxygen, high-flow oxygen support, or NIPPV **Key Exclusion Criteria:** • Requiring IMV • Pregnancy • Confirmed bacterial pneumonia or active/uncontrolled fungal or viral infection • Not expected to survive the 48 hours following randomization • Use of IL-1 inhibitors, IL-6 inhibitors, kinase inhibitors, or SARS-CoV-2 neutralizing monoclonal antibodies within prior 8 weeks	**Number of Participants:** • mITT (n = 479): lenzilumab (n = 236) and placebo (n = 243) **Participant Characteristics:** • Mean age was 60.5 years. • 64.7% were men. • 43.2% were White. • 55.1% had a BMI ≥30. • 40.5% received high-flow oxygen support or NIPPV at baseline. • 93.7% received corticosteroids; 72.4% received RDV; 69.1% received both corticosteroids and RDV. **Primary Outcome:** • Lenzilumab improved ventilator-free survival through Day 28: • mITT participants: HR 1.54; 95% CI, 1.02–2.31; *P* = 0.041 • ITT participants: HR 1.90; 95% CI, 1.02–3.52; *P* = 0.043	**Key Limitations:** • The study was not powered to detect a survival benefit. • There were differences in access to supportive care across the study sites. **Interpretation:** • In this large, unpublished, placebo-controlled study, lenzilumab improved ventilator-free survival in participants who were hypoxic but not mechanically ventilated.

Study Design	Methods	Results	Limitations and Interpretation
Lenzilumab in Hospitalized Patients With COVID-19 Pneumonia (LIVE-AIR Trial)[2], continued			
	Interventions *1:1 Randomization:* • Lenzilumab 600 mg IV every 8 hours for 3 doses • Placebo **Primary Endpoint:** • Ventilator-free survival through Day 28 (composite endpoint of time to death and time to IMV) **Key Secondary Endpoints:** • Survival • Proportion of IMV, ECMO, or death • Time to recovery	• Kaplan-Meier estimate for proportion of participants who had required IMV or died through Day 28: • mITT lenzilumab arm: 15.6% (95% CI, 11.5–21.0); placebo arm: 22.1% (95% CI, 17.4–27.9) • ITT lenzilumab arm: 18.9% (95% CI, 14.5–24.3); placebo arm: 23.6% (95% CI, 18.8–29.3) • Primary outcome sensitivity mITT analyses showed lenzilumab improved the likelihood of ventilator-free survival in participants: • Aged <85 years with CRP <150 mg/L (n = 336): HR 2.96; 95% CI, 1.63–5.37; $P = 0.0003$ • Receiving corticosteroids plus RDV (n = 331): HR 1.92; 95% CI, 1.20–3.07; $P = 0.0067$ • Hospitalized ≤2 days prior to randomization (n = 297): HR 1.88; 95% CI, 1.13–3.12; $P = 0.015$ **Key Secondary Outcomes:** • No difference in proportion of participants who died: 9.6% in lenzilumab arm vs. 13.9% in placebo arm (HR 1.38; 95% CI, 0.81–2.37; $P = 0.239$) • No difference between the arms in the incidence of IMV, ECMO, or death: HR 0.67; 95% CI, 0.41–1.10; $P = 0.111$ • No difference between the arms in time to recovery: HR 1.09; 95% CI, 0.88–1.35; $P = 0.43$)	
Mavrilimumab in Patients With Severe COVID-19 Pneumonia and Systemic Hyperinflammation (MASH-COVID Trial)[3]			
Multicenter, double-blind RCT in hospitalized patients with COVID-19 pneumonia in the United States (n = 40)	**Key Inclusion Criteria:** • Hospitalization with SARS-CoV-2 pneumonia • Hypoxemia (SpO_2 <92% or requirement for supplemental oxygen) • CRP >5 mg/dL	**Number of Participants:** • Mavrilimumab (n = 21) and placebo (n = 19) • Study enrollment was from May 28–September 15, 2020. **Participant Characteristics:** • 65% were men. • 40% were African American.	**Key Limitations:** • The small sample size resulted in low power to identify a clinically meaningful treatment effect. • The study was stopped early due to slow enrollment.

Study Design	Methods	Results	Limitations and Interpretation
Mavrilimumab in Patients With Severe COVID-19 Pneumonia and Systemic Hyperinflammation (MASH-COVID Trial)[3], continued			
Multicenter, double-blind RCT in hospitalized patients with COVID-19 pneumonia in the United States (n = 40)	**Key Exclusion Criteria:** • Mechanical ventilation • ANC <1,500/mm^3 • Uncontrolled bacterial infection **Interventions** *1:1 Randomization:* • Mavrilimumab 6 mg/kg as a single IV infusion • Placebo **Primary Endpoint:** • Proportion of participants alive and off supplemental oxygen at Day 14 **Key Secondary Endpoints:** • Survival at Day 28 • Respiratory failure-free survival at Day 28	• 50% required nasal high-flow oxygen or noninvasive ventilation. • Corticosteroids use: 67% in the mavrilimumab arm, 63% in the placebo arm • RDV use: 76% in the mavrilimumab arm, 74% in the placebo arm **Primary Outcome:** • No significant difference in primary outcome: 12 of 21 participants (57%) in the mavrilimumab arm vs. 9 of 19 participants (47%) in the placebo arm (OR 1.48; 95% CI, 0.43–5.16; *P* = 0.76) **Key Secondary Outcomes:** • No difference in survival: 1 participant in the mavrilimumab arm vs. 3 in the placebo arm had died by Day 28 (HR 3.72; 95% CI, 0.39–35.79; *P* = 0.22) • No difference in respiratory failure free survival at Day 28: 20 participants (95%) in the mavrilimumab arm vs. 15 (79%) in the placebo arm (OR 5.33; 95% CI, 0.54–52.7; *P* = 0.43)	**Interpretation:** • In this small study, no differences in outcomes were observed between the mavrilimumab and placebo arms among participants who were not mechanically ventilated.

Key: ANC = absolute neutrophil count; BMI = body mass index; CRP = C-reactive protein; ECMO = extracorporeal membrane oxygenation; GM-CSF = granulocyte macrophage-colony stimulating factor; ICU = intensive care unit; IL = interleukin; IMV = invasive mechanical ventilation; ITT = intention-to-treat; IV = intravenous; mITT = modified intention-to-treat; NIPPV = noninvasive positive pressure ventilation; the Panel = the COVID-19 Treatment Guidelines Panel; 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 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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Interferons (Alfa, Beta)

Last Updated: August 27, 2020

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

Recommendation

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

Rationale

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

Clinical Data for COVID-19

Interferon Beta-1a

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

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

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

An open-label, Phase 2 clinical trial randomized 127 participants (median age of 52 years) 2:1 to combination antiviral therapy or lopinavir/ritonavir. In the combination antiviral therapy group, the treatment regimen differed by time from symptom onset to hospital admission. Participants hospitalized within 7 days of symptom onset (n = 76) were randomized to triple drug therapy (interferon beta-1b 8 million units administered subcutaneously every other day for up to 7 days total, lopinavir/ritonavir, and ribavirin); those hospitalized ≥7 days after symptom onset (n = 51) were randomized to double therapy (lopinavir/ritonavir and ribavirin) because of concerns regarding potential inflammatory effects of interferon. Patients in the control group received lopinavir/ritonavir alone regardless of the time from symptom onset to hospitalization. The study participants were patients in Hong Kong with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection who were hospitalized, regardless of disease severity, until they had two negative nasopharyngeal (NP) swab tests.

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

Interferon Alfa-2b

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

Clinical Data for SARS and MERS

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

In a retrospective observational analysis of 350 critically ill patients with MERS[6] from 14 hospitals in Saudi Arabia, the mortality rate was higher among patients who received ribavirin and interferon (beta-1a, alfa-2a, or alfa-2b) than among those who did not receive either drug.

A randomized clinical trial that included 301 patients with acute respiratory distress syndrome[10] found that intravenous interferon beta-1a had no benefit over placebo as measured by ventilator-free days over a 28-day period (median of 10.0 days in the interferon beta-1a group vs. 8.5 days in the placebo group) or mortality (26.4% in the interferon beta-1a group vs. 23.0% in the placebo group).

Clinical Trials

See ClinicalTrials.gov for a list of ongoing clinical trials for interferon and COVID-19.

Adverse Effects

The most frequent adverse effects of interferon alfa include flu-like symptoms, nausea, fatigue, weight loss, hematological toxicities, elevated transaminases, and psychiatric problems (e.g., depression and suicidal ideation). Interferon beta is better tolerated than interferon alfa.[11,12]

Drug-Drug Interactions

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

Considerations in Pregnancy

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

Considerations in Children

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

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Interleukin-1 Inhibitors

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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)**.

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

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 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]

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 two 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, or invasive 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 **(BI)**.

Additional Considerations

- Tocilizumab and sarilumab **should be used with caution** in groups of patients with COVID-19 that have not been adequately studied in clinical trials. This includes patients who are significantly immunosuppressed, particularly those who have recently received other biologic immunomodulating drugs, and those with:
  - 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 the drug
- 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 decide to assess the patient's clinical response to dexamethasone before deciding whether tocilizumab or sarilumab is needed.
- In both the REMAP-CAP trial and the RECOVERY trial, 29% of patients received a second dose of tocilizumab at the discretion of the treating physicians. However, the available data are currently insufficient to recommend either for or against a second dose.[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 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]

Rationale

The results of the RECOVERY and REMAP-CAP trials provide consistent evidence that tocilizumab, when administered 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 for the efficacy of tocilizumab is more extensive than that 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 a 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 4d.

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).[12-14] For example, trials that reported a treatment benefit of tocilizumab enrolled patients who were receiving higher levels of oxygen support (e.g., high-flow nasal cannula oxygen, noninvasive ventilation, invasive mechanical ventilation) and/or included more patients who used corticosteroids.[15,16] Subsequently, the REMAP-CAP and RECOVERY trials—the two largest randomized controlled tocilizumab trials—both reported a mortality benefit of tocilizumab in certain patients, including patients exhibiting rapid respiratory decompensation associated with an inflammatory response. REMAP-CAP enrolled a narrowly defined population of critically ill patients who were enrolled within 24 hours of starting respiratory support in an intensive care unit and who were randomized to receive open-label tocilizumab or usual care.[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 also had hypoxemia and CRP levels ≥75 mg/L were offered enrollment into a second randomization that evaluated tocilizumab versus usual care. 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 can be found in Therapeutic Management of Hospitalized Adults With COVID-19.

The Panel's recommendations for using tocilizumab are based on the collective evidence from the clinical trials reported to date (see Table 4d).

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 study controls. Additional adverse effects, such as serious infections (e.g., tuberculosis [TB], bacterial or fungal infections) and bowel perforation, have been reported.[17]

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 utero in the exposed fetus. Given the paucity of data, current recommendations advise against the use of tocilizumab during pregnancy.[18] The decision to use tocilizumab during pregnancy should be a collaborative effort between pregnant individuals and their health care providers, 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 available on the effectiveness of tocilizumab for the treatment of COVID-19 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.[19] 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, noninvasive or invasive 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, one 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 4d.

An adaptive Phase 2 and 3 double-blind, placebo-controlled randomized (2:2:1) 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 that was conducted in the United States in patients with severe and critical COVID-19 also failed to show a benefit of sarilumab. In this trial, there was a numerical decrease in mortality among participants with critical COVID-19 pneumonia who required mechanical ventilation and who received corticosteroids; however, because of the small sample size in this study, the 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 who were randomized to receive sarilumab (n = 485) had more organ support-free days (OR 1.50; 95% CrI, 1.13–2.00) and better survival rates 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 patients who received sarilumab (i.e., randomization for the standard of care arm closed on November 19, 2020, and randomization for the sarilumab arm continued through April 10, 2021).[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 utero in the exposed fetus.

Considerations in Children

There are no data on the use of sarilumab in children other than data from ongoing trials that are assessing the drug's safety in children with juvenile idiopathic arthritis. There are no systematic observational or randomized controlled trial data available on the efficacy of sarilumab for the treatment of COVID-19 or MIS-C in children.

Drug Availability

The IV formulation of sarilumab is not approved by the FDA, but it is being studied in a clinical trial of hospitalized patients with COVID-19. In the REMAP-CAP trial, a single SQ dose of sarilumab 400 mg was reconstituted in 100 cc 0.9% NaCl and given as an IV infusion over a 1-hour period.[22]

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.

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 utero 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 4d. Interleukin-6 Inhibitors: Selected Clinical Data

Last Updated October 19, 2021

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.

Methods	Results	Limitations and Interpretation
RECOVERY Trial: Open-Label RCT of Tocilizumab and Usual Care in Hospitalized Patients With COVID-19[1]		
Key Inclusion Criteria: • SpO_2 <92% on room air or receipt of supplemental oxygen • CRP ≥75 mg/L **Key Exclusion Criteria:** • 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 alive • Among those not on IMV at enrollment, receipt of IMV or death	**Participant Characteristics:** • Mean age 63.6 years; 67% male; 76% White • 95% had PCR-confirmed SARS-CoV-2 infection • At baseline: • 45% on conventional oxygen • 41% on HFNC or noninvasive ventilation • 14% on IMV • 82% on corticosteroids **Primary Outcomes:** • Day 28 mortality was lower in tocilizumab arm than in usual care arm (31% vs. 35%; rate ratio 0.85; 95% CI, 0.76–0.94; *P* = 0.003). • Among those who required IMV at baseline, Day 28 mortality was similar between arms (49% in tocilizumab arm vs. 51% in usual care arm; risk ratio 0.93; 95% CI, 0.74–1.18). **Secondary Outcomes:** • Proportion of patients discharged alive within 28 days was greater in tocilizumab arm (57% vs. 50%; rate ratio 1.22; 95% CI, 1.12–1.33; *P* < 0.0001). • Among those not on IMV at baseline, the percentage of patients who died or required IMV was lower in tocilizumab arm than usual care arm (35% vs. 42%; rate ratio 0.84; 95% CI, 0.77–0.92; *P* < 0.0001).	**Key Limitations:** • Arbitrary enrollment cut off at CRP ≥75 mg/L • Difficult to define exact subset of patients in RECOVERY cohort who were subsequently selected for secondary randomization/tocilizumab trial **Interpretation:** • Among hospitalized patients with hypoxemia and elevated CRP, tocilizumab was associated with reduced all-cause mortality and shorter time to discharge.

Methods	Results	Limitations and Interpretation
REMAP-CAP: Open-Label, Adaptive Platform RCT of Tocilizumab and Sarilumab in Patients With COVID-19[2,3]		
Key Inclusion Criteria: • ICU admission • Suspected or laboratory-confirmed COVID-19 • Receipt of IMV, noninvasive ventilation, or cardiovascular support **Key Exclusion Criteria:** • >24 hours since ICU admission • Presumption of imminent death • Immunosuppression • ALT >5 times ULN **Interventions:** • Single dose of tocilizumab 8 mg/kg and possible second dose, plus SOC (n = 952) • Single dose of sarilumab 400 mg IV plus SOC (n = 485) • SOC (n = 406) **Randomization:** • Adaptative randomization. Patients were randomized to receive SOC only, SOC plus tocilizumab, or SOC plus sarilumab based on provider preference, availability, or adaptive probability. SOC arm was closed in November 2020 (n = 366 for tocilizumab, n = 48 for sarilumab, n = 412 for SOC). • After November 2020, patients were randomized mostly to receive tocilizumab, sarilumab, or anakinra until April 10, 2021.	**Participant Characteristics:** • Mean age 60 years; 69% male; 75% White • 86% had PCR-confirmed SARS-CoV-2 infection • Median time from ICU admission until enrollment was 14 hours • At baseline: • 67% on HFNC or noninvasive ventilation • 33% on IMV • 67% on corticosteroids in control arm, 82% in tocilizumab arm, and 89% in sarilumab arm **Primary Outcomes** *Tocilizumab Versus SOC:* • Median number of organ support-free days was 7 in tocilizumab arm and 0 in SOC arm. • Median adjusted OR for ordinal scale was 1.46 (95% CrI, 1.13–1.87). • In highest CRP tercile, aOR was 1.87 (95% CrI, 1.35–2.59). • Outcomes were consistent across subgroups of oxygen requirements at study entry. *Sarilumab Versus SOC:* • Median number of organ support-free days was 9 in sarilumab arm and 0 in SOC arm. • Median adjusted OR for ordinal scale was 1.50 (95% CrI, 1.13–2.00). • In highest CRP tercile, aOR was 1.85 (95% CrI, 1.24–2.69). • Outcomes were consistent across subgroups of oxygen requirements at study entry.	**Key Limitation:** • Enrollment in tocilizumab and sarilumab arms was partially nonconcurrent with SOC arm; while the comparisons to 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. • 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.

Methods	Results	Limitations and Interpretation
REMAP-CAP: Open-Label, Adaptive Platform RCT of Tocilizumab and Sarilumab in Patients With COVID-19[2,3], continued		
Primary Endpoint: • Composite endpoint measured using an ordinal scale that combined mortality and days free of respiratory or cardiovascular support to Day 21 **Key Secondary Endpoint:** • In-hospital survival	**Secondary Outcomes** *Tocilizumab Versus SOC:* • In-hospital survival was 66% in tocilizumab arm and 63% in SOC arm (aOR 1.42; 95% CrI, 1.05–1.93). *Sarilumab Versus SOC:* • In-hospital survival was 67% in sarilumab arm and 63% in SOC arm (aOR 1.51; 95% CrI, 1.06–2.20).	
COVACTA: Double-Blind RCT of Tocilizumab in Hospitalized Patients With COVID-19[4]		
Key Inclusion Criteria: • PCR-confirmed SARS-CoV-2 infection • Hypoxemia • Bilateral chest infiltrates **Key Exclusion Criteria:** • Death imminent • Active infection other than SARS-CoV-2 **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 (measured using ordinal scale) **Key Secondary Endpoints:** • Time to discharge • Length of ICU stay • Day 28 mortality	**Participant Characteristics:** • Mean age 61 years; 70% male; 58% White • 30% on HFNC or noninvasive ventilation • 14% on IMV • 25% with multiorgan failure • 36% in tocilizumab arm and 55% in placebo arm received corticosteroids at entry or during follow-up **Primary Outcome:** • No significant difference between arms in clinical status at Day 28. **Secondary Outcomes:** • Shorter median time to discharge in tocilizumab arm than placebo arm (20 vs. 28 days; HR 1.35; 95% CI, 1.02–1.79). • Shorter median ICU stay in tocilizumab arm than placebo arm (9.8 vs. 15.5 days). • No difference in Day 28 mortality between arms (19.7% in tocilizumab arm vs. 19.4% placebo).	**Key Limitations:** • Modest power to detect differences in Day 28 clinical status • Corticosteroids used by more patients in placebo arm than tocilizumab arm • Few patients on IMV **Interpretation:** • There was no difference between arms at Day 28 clinical status or survival. • Patients in tocilizumab arm had shorter median times for recovery and ICU stay than those in placebo arm.

Methods	Results	Limitations and Interpretation
EMPACTA: Double-Blind RCT of Tocilizumab in Hospitalized Patients With COVID-19[5]		
Key Inclusion Criteria: • PCR-confirmed SARS-CoV-2 infection • COVID-19 pneumonia **Key Exclusion Criteria:** • Noninvasive ventilation or IMV **Interventions:** • Single dose of tocilizumab 8 mg/kg plus SOC, possible second dose (n = 249) • Placebo plus SOC (n = 128) **Primary Endpoint:** • IMV, ECMO, or death by Day 28 **Key Secondary Endpoints:** • Time to hospital discharge or readiness for discharge (measured using ordinal scale) • All-cause mortality by Day 28	**Participant Characteristics:** • Mean age 56 years; 59% male; 56% Hispanic/Latinx, 15% Black/African American, 13% American Indian/Alaska Native • 84% with elevated CRP • Concomitant medications: • 80% on corticosteroids and 53% on RDV in tocilizumab arm • 88% on corticosteroids and 59% on RDV in placebo arm **Primary Outcome:** • Proportion of patients who required IMV or ECMO or who died by Day 28 was 12% in tocilizumab arm and 19% in placebo arm (HR 0.56; 95% CI, 0.33–0.97; *P* = 0.04). **Key Secondary Outcomes:** • Median number of days to hospital discharge or readiness for discharge was 6.0 in tocilizumab arm and 7.5 in placebo arm (HR 1.16; 95% CI, 0.91–1.48). • All-cause mortality by Day 28 was not statistically different between arms (10.4% in tocilizumab arm vs. 8.6% in placebo arm).	**Key Limitation:** • Moderate sample size **Interpretation:** • Among patients with COVID-19 pneumonia, tocilizumab lowered rates of IMV, ECMO, or death by Day 28 but provided no benefit for 28-day mortality.
BACC Bay: Double-Blind RCT of Tocilizumab in Hospitalized Patients With COVID-19[6]		
Key Inclusion Criteria: • Laboratory-confirmed SARS-CoV-2 infection • ≥2 of the following conditions: • Fever >38°C • Pulmonary infiltrates • Need for 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	**Participant Characteristics:** • Median age 60 years; 58% male; 45% Hispanic/Latinx • 50% with BMI ≥30; 49% with HTN; 31% with diabetes • 80% receiving oxygen ≤6 L/min; 4% receiving high-flow oxygen; 16% receiving no supplemental oxygen • Concomitant medications: • 11% on corticosteroids and 33% on RDV in tocilizumab arm • 6% on glucocorticoids and 29% on RDV in placebo arm **Primary Outcome:** • No difference between arms in Day 28 intubation or death (10.6% in tocilizumab arm vs. 12.5% in placebo arm; HR 0.83; 95% CI, 0.38–1.81; *P* = 0.64).	**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 intubation 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.

Methods	Results	Limitations and Interpretation
BACC Bay: Double-Blind RCT of Tocilizumab in Hospitalized Patients With COVID-19[6], continued		
Interventions: • Tocilizumab 8 mg/kg plus usual care (n = 161) • Placebo plus usual care (n = 81) **Primary Endpoint:** • Intubation or death, according to a time to event analysis; data censored at Day 28 **Key Secondary Endpoints:** • Clinical worsening by Day 28, based on an ordinal scale • Discontinuation of supplemental oxygen among patients receiving it at baseline	**Key Secondary Outcomes:** • No difference between arms in proportion of patients who experienced worsening of disease by Day 28 (19% in tocilizumab arm vs. 17% in placebo arm; HR 1.11; 95% CI, 0.59–2.10). • Median number of days to discontinuation of oxygen was 5.0 in tocilizumab arm and 4.9 in placebo arm (P = 0.69).	
Double-Blind, RCT of Sarilumab in Hospitalized Patients With Severe or Critical COVID-19[7]		
Key Inclusion Criteria: • Aged ≥18 years • Severe or critical laboratory-confirmed COVID-19 • COVID-19 pneumonia **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% male; 77% White; 36% Hispanic/Latinx • 39% on HFNC, IMV, or noninvasive mechanical ventilation • 42% with BMI ≥30; 43% with HTN; 26% with type 2 diabetes • 20% received systemic corticosteroids before receiving intervention **Primary Outcome:** • No difference in median time to clinical improvement among the sarilumab arms (10 days for each) and placebo arm (12 days). **Key Secondary Outcome:** • No difference among the arms in survival at Day 29 (92% in placebo arm vs. 90% in sarilumab 200 mg arm vs. 92% in sarilumab 400 mg arm).	**Key Limitations:** • Only 20% of patients received corticosteroids • Moderate sample size and a small placebo arm **Interpretation:** • There was no benefit of sarilumab in hospitalized adults with COVID-19 in time to clinical improvement or mortality. This could be due to the low rate of concomitant corticosteroid use among the study participants.

Key: ALT = alanine transaminase; BMI = body mass index; CRP = C-reactive protein; ECMO = extracorporeal membrane oxygenation; HFNC = high-flow nasal cannula; HTN = hypertension; ICU = intensive care unit; IL = interleukin; IMV = invasive mechanical ventilation; IV = intravenous; LDH = lactate dehydrogenase; 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: October 19, 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 hospitalized patients who require high-flow oxygen or noninvasive ventilation.
- 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 invasive mechanical ventilation. However, a key limitation of the ACTT-2 trial is that corticosteroids were not used as 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 one elevated inflammatory marker at enrollment who were not on invasive 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 anti-tumor necrosis factor inhibitors in people with rheumatoid arthritis found that tofacitinib was associated with additional serious adverse 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 2 mg once daily dose 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, invasive 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 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 eight-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 one 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 invasive 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, invasive 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). The occurrence of adverse events, serious adverse events, serious infections, and venous thromboembolic events was comparable in the baricitinib and placebo arms.[6]

Additional findings from the ACTT-2 and COV-BARRIER trials and the rationale for using baricitinib in certain hospitalized patients with COVID-19 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.

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, invasive 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.[19] Tofacitinib is also FDA approved for the treatment of psoriatic arthritis, juvenile idiopathic arthritis, and ulcerative colitis.[20]

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.[21] 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, randomized controlled Phase 2 trial in patients with COVID-19 in China compared ruxolitinib 5 mg orally twice daily (n = 20) with placebo (administered as vitamin C 100 mg; n = 21), both given in combination with 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 two-point improvement on a seven-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.[22] A Phase 3 trial of ruxolitinib in patients with COVID-19-associated acute respiratory distress syndrome is currently in progress (ClinicalTrials.gov Identifier NCT04377620).

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.[23] 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.[24] 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[25] and to prevent chronic graft-versus-host disease in stem cell transplant recipients.[26] 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.[27]

Clinical Data for COVID-19

Data regarding ibrutinib are limited to those from an uncontrolled, retrospective case series of six patients with COVID-19 who were receiving the drug for a condition other than COVID-19.[27] 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.[28] 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.[29] Zanubrutinib is proposed to benefit patients with COVID-19 by modulating signaling that promotes inflammation.

Clinical Data for COVID-19

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

Clinical Trials

Please 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.[25,30] 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 4e. Characteristics of Immunomodulators Under Evaluation for the Treatment of COVID-19

Last Updated: October 19, 2021

- The information in this table is derived from data on the use of these drugs for FDA-approved indications or in investigational trials, and it is supplemented with data on their use in patients with COVID-19, when available.
- For dose modifications for patients with organ failure or those who require extracorporeal devices, please refer to product labels, when available.
- There are currently not enough data to determine whether certain medications can be safely coadministered with therapies for the treatment of COVID-19. When using concomitant medications with similar toxicity profiles, consider performing additional safety monitoring.
- The potential additive, antagonistic, or synergistic effects and the safety of using certain combination therapies for the treatment of COVID-19 are unknown. Clinicians are encouraged to report AEs to the FDA *Medwatch* program.
- For the Panel's recommendations on using the drugs listed in this table, please refer to the drug-specific sections of the Guidelines and to Therapeutic Management of Hospitalized Adults With COVID-19.

Drug Name	Dosing Regimen *The doses listed are for approved indications, from clinical trials or clinical experience for COVID-19.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Colchicine					
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]	• Diarrhea • Nausea • Vomiting • Cramping • Abdominal pain • Bloating • Loss of appetite • Neuromyotoxicity (rare)[2] • 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, and those with moderate renal insufficiency should be monitored for AEs. • A list of clinical trials is available: Colchicine **Availability:** • In the COLCORONA trial, 0.5 mg colchicine tablets were used for dosing; in the United States, colchicine is available as 0.6 mg tablets.

Drug Name	Dosing Regimen *The doses listed are for approved indications, from clinical trials or clinical experience for COVID-19.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Corticosteroids					
Budesonide (Inhaled)	**Dose for COVID-19 in Clinical Trials:** • Budesonide 800 mcg inhaled twice daily until symptom resolution or for up to 14 days[3,4]	• Secondary infections • Oral thrush • Systemic adverse effects (less common)	• Signs of adverse effects 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
Dexamethasone (Systemic)	**Dose for COVID-19:** • Dexamethasone 6 mg IV or PO once daily for up to 10 days or until hospital discharge, whichever comes first[5]	• Hyperglycemia • Secondary infections • Reactivation of latent infections (e.g., HBV, HSV, strongyloidiasis, TB) • 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 • Cases of disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with corticosteroids and tocilizumab. Prophylactic treatment for strongyloidiasis (e.g., with IVM) should be considered for persons from areas where *Strongyloides* is endemic.[6]	• Moderate CYP3A4 inducer • CYP3A4 substrate • Although coadministration of RDV and dexamethasone has not been formally studied, a clinically significant PK interaction is not predicted (Gilead, written communication, August 2020).	• If dexamethasone is not available, an alternative corticosteroid (e.g., prednisone, methylprednisolone, hydrocortisone) can be used. • The approximate total daily dose equivalencies for these glucocorticoids to dexamethasone 6 mg (PO or IV) are: prednisone 40 mg, methylprednisolone 32 mg, and hydrocortisone 160 mg. • A list of clinical trials is available: Dexamethasone

Drug Name	Dosing Regimen *The doses listed are for approved indications, from clinical trials or clinical experience for COVID-19.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Fluvoxamine					
Fluvoxamine	**Dose for COVID-19 in Clinical Trials:** • Various dosing regimens used	• Nausea • Diarrhea • Dyspepsia • Asthenia • Insomnia • Somnolence • Sweating • Suicidal ideation (rare)	• Hepatic function • Drug interactions • Monitor for withdrawal symptoms when tapering dose.	• CYP2D6 substrate • Fluvoxamine inhibits several CYP450 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
Granulocyte-Macrophage Colony-Stimulating Factor Inhibitors					
Lenzilumab	**Dose for COVID-19 in Clinical Trial:** • Lenzilumab 600 mg IV infusion every 8 hours times 3 doses[7]	• No treatment-emergent SAEs were reported in clinical trials.	• CBC with differential • Liver enzymes • Infusion reactions • HSR	• Data not available	• A list of clinical trials is available: Lenzilumab
Mavrilimumab	**Dose for COVID-19 in Clinical Trial:** • Mavrilimumab 6 mg/kg IV infusion once[8]	• No treatment-emergent SAEs were reported in clinical trials.	• CBC with differential • Liver enzymes • Infusion reactions • HSR	• Data not available	• A list of clinical trials is available: Mavrilimumab
Otilimab	**Dose for COVID-19 in Clinical Trial:** • Otilimab 90 mg IV infusion once[9]	• No treatment-emergent SAEs were reported in clinical trials.	• CBC with differential • Liver enzymes • Infusion reactions • HSR	• Data not available	• A list of clinical trials is available: Otilimab

Drug Name	**Dosing Regimen** *The doses listed are for approved indications, from clinical trials or clinical experience for COVID-19.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Interferons					
Interferon Alfa	**Peg-IFN Alfa-2a** *Dose for MERS:* • Peg-IFN alfa-2a 180 μg SQ once weekly for 2 weeks[10,11] **IFN Alfa-2b** *Dose for COVID-19 in Clinical Trial:* • Nebulized IFN alfa-2b 5 million international units twice daily (no duration listed in the study methods)[12]	• Flu-like symptoms (e.g., fever, fatigue, myalgia)[13] • Injection site reactions • Liver function abnormalities • Decreased blood counts • Worsening depression • Insomnia • Irritability • Nausea • Vomiting • HTN • Induction of autoimmunity	• CBC with differential • Liver enzymes; **avoid** use if Child-Pugh Score >6. • Renal function; reduce dose if CrCl <30 mL/min. • Depression, psychiatric symptoms	• Low potential for drug-drug interactions • Inhibition of CYP1A2	• For COVID-19, IFN alfa has primarily been used as nebulization and usually as part of a combination regimen. • **Use with caution** with other hepatotoxic agents. • Reduce dose if ALT >5 times ULN; discontinue if bilirubin level also increases. • Reduce dose or discontinue if neutropenia or thrombocytopenia occur. • A list of clinical trials is available: Interferon **Availability:** • Neither nebulized IFN alfa-2b nor IFN alfa-1b are FDA-approved for use in the United States.

Drug Name	**Dosing Regimen** *The doses listed are for approved indications, from clinical trials or clinical experience for COVID-19.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Interferons, continued					
Interferon Beta	**IFN Beta-1a** *Dose for MERS:* • IFN beta-1a 44 mcg SQ 3 times weekly[11] *Dose for COVID-19:* • Dose and duration unknown **IFN Beta-1b** *Dose for COVID-19 in Clinical Trial:* • IFN beta-1b 8 million international units SQ every other day, up to 7 days total[14]	• Flu-like symptoms (e.g., fever, fatigue, myalgia)[15] • Leukopenia, neutropenia, thrombocytopenia, lymphopenia • Liver function abnormalities (elevation of ALT > of 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 **Availability:** • Several IFN-beta products are available in the United States; product doses differ. *IFN Beta-1a Products:* • Avonex, Rebif *IFN Beta-1b Products:* • Betaseron, Extavia

Drug Name	**Dosing Regimen** *The doses listed are for approved indications, from clinical trials or clinical experience for COVID-19.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Interleukin-1 Inhibitors					
Anakinra	**Dose for Rheumatoid Arthritis:** • Anakinra 100 mg SQ once daily **Dose for COVID-19 in Clinical Trials:** • Dose and duration vary by study • Has also been used as IV infusion	• Neutropenia (particularly with concomitant use of other agents that can cause neutropenia) • Anaphylaxis 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.	• A list of clinical trials is available: Anakinra • Anakinra for IV administration is not an approved formulation in the United States.[16]
Canakinumab	**Dose for Systemic Juvenile Idiopathic Arthritis:** • Canakinumab 4 mg/kg (maximum 300 mg) SQ every 4 weeks[17] **Dose for COVID-19 in Clinical Trials:** • Dose and duration vary by study *CAN-COVID Trial:* • Single weight-based dose of canakinumab in 250 mL of 5% dextrose by IV infusion over 2 hours:[18] • 40 to <60 kg: 450 mg • 60–80 kg: 600 mg • >80 kg: 750 mg	• 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 CYP450 enzymes and alter metabolism of drugs that are CYP450 substrates. • Use with TNF-blocking agents **is not recommended** due to potential increased risk of infection. • **Avoid** concomitant administration of live vaccines.	• A list of clinical trials is available: Canakinumab • Canakinumab for IV administration is not an approved formulation in the United States.[17]

Drug Name	**Dosing Regimen** *The doses listed are for approved indications, from clinical trials or clinical experience for COVID-19.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Interleukin-6 Inhibitors					
Anti-Interleukin-6 Receptor Monoclonal Antibodies					
Sarilumab[19]	**Dose for COVID-19 in Clinical Trials:** • Single dose of sarilumab 400 mg IV[20] • The only FDA-approved route of administration for sarilumab is SQ. In the REMAP-CAP trial, an SQ formulation of sarilumab 400 mg (in a prefilled syringe) was reconstituted in 100 mL 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.[21]	• 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 CYP450 enzymes; thus, use of sarilumab may lead to increased metabolism of drugs that are CYP450 substrates. • The effects of sarilumab on CYP450 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:** • Sarilumab for IV administration is not an approved formulation in the United States. • In the REMAP-CAP trial, SQ formulations of sarilumab were reconstituted for IV administration.[21]

Drug Name	**Dosing Regimen** *The doses listed are for approved indications, from clinical trials or clinical experience for COVID-19.*	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[22]	**EUA Dose for COVID-19** *For Hospitalized Patients Aged ≥2 Years Based on Body Weight:* • Weighing <30 kg: Tocilizumab 12 mg/kg administered by IV infusion over 1 hour • Weighing ≥30 kg: Tocilizumab 8 mg/kg (maximum dose 800 mg) administered 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 of tocilizumab may be administered at least 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	• HSR • Infusion reactions • Neutrophils • Platelets • Liver enzymes • Cases of disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with tocilizumab and corticosteroids. Prophylactic treatment for strongyloidiasis (e.g., with IVM) should be considered for persons from areas where *Strongyloides* is endemic.[6]	• Elevated IL-6 may downregulate CYP enzymes; use of tocilizumab may lead to increased metabolism of drugs that are CYP450 substrates. • The effects of tocilizumab on CYP450 enzymes may persist for weeks after the drug is stopped.	• Tocilizumab use **should be avoided** in patients who are significantly immunocompromised. The safety of using tocilizumab plus a corticosteroid in immunocompromised patients is unknown. • The SQ 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, noninvasive mechanical ventilation, IMV, or ECMO. The EUA does not authorize the use of tocilizumab for SQ administration for the treatment of COVID-19.[23]

Drug Name	Dosing Regimen *The doses listed are for approved indications, from clinical trials or clinical experience for COVID-19.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Interleukin-6 Inhibitors, continued					
Anti-Interleukin-6 Monoclonal Antibody					
Siltuximab	**Dose for Multicentric Castleman Disease:** • Siltuximab 11 mg/kg administered over 1 hour by IV infusion every 3 weeks[24] **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 CYP450 substrates. • Effects on CYP450 may persist for weeks after therapy.	• Treatment with siltuximab may mask signs of acute inflammation or infection (i.e., by suppressing fever and CRP levels). • A list of clinical trials is available: Siltuximab
Kinase Inhibitors					
Bruton's Tyrosine Kinase Inhibitors					
Acalabrutinib	**Dose for FDA-Approved Indications:** • Acalabrutinib 100 mg PO every 12 hours **Dose for COVID-19:** • Dose and duration unknown	• Hemorrhage • Cytopenias (i.e., neutropenia, anemia, thrombocytopenia, lymphopenia) • Atrial fibrillation and flutter • Infection • Headache • Diarrhea • Fatigue • Myalgia	• CBC with differential • Signs and symptoms of bleeding (particularly when coadministered with anticoagulant or antiplatelet therapy) • Cardiac arrhythmias • New infections	• **Avoid** concomitant use with strong CYP3A inhibitors or inducers. • Dose reduction may be necessary with moderate CYP3A4 inhibitors. • **Avoid** concomitant PPI use. • H2-receptor antagonists should be administered 2 hours after acalabrutinib.	• **Avoid** use in patients with severe hepatic impairment. • Patients with underlying cardiac risk factors, HTN, or acute infections may be predisposed to atrial fibrillation. • A list of clinical trials is available: Acalabrutinib

Drug Name	Dosing Regimen *The doses listed are for approved indications, from clinical trials or clinical experience for COVID-19.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Kinase Inhibitors, continued					
Bruton's Tyrosine Kinase Inhibitors, continued					
Ibrutinib	**Dose for FDA-Approved Indications:** • Ibrutinib 420 mg or 560 mg PO once daily **Dose for COVID-19:** • Dose and duration unknown	• Hemorrhage • Cardiac arrhythmias • Serious infections • Cytopenia (i.e., thrombocytopenia, neutropenia, anemia) • HTN • Diarrhea • Musculoskeletal pain • Rash	• CBC with differential • BP • Signs and symptoms of bleeding (particularly when coadministered with anticoagulant or antiplatelet therapy) • Cardiac arrhythmias • New infections	• **Avoid** concomitant use with strong CYP3A inhibitors or inducers. • Dose reduction may be necessary with moderate CYP3A4 inhibitors.	• **Avoid** use in patients with severe baseline hepatic impairment. Dose modifications required in patients with mild or moderate hepatic impairment. • Patients with underlying cardiac risk factors, HTN, or acute infections may be predisposed to cardiac arrhythmias. • A list of clinical trials is available: Ibrutinib
Zanubrutinib	**Dose for FDA-Approved Indications:** • Zanubrutinib 160 mg PO twice daily or 320 mg PO once daily **Dose for COVID-19:** • Dose and duration unknown	• Hemorrhage • Cytopenias (i.e., neutropenia, thrombocytopenia, anemia, leukopenia) • Atrial fibrillation and flutter • Infection • Rash • Bruising • Diarrhea • Cough • Musculoskeletal pain	• CBC with differential • Signs and symptoms of bleeding • Cardiac arrhythmias • New infections	• **Avoid** concomitant use with moderate or strong CYP3A inducers. • Dose reduction required with moderate and strong CYP3A4 inhibitors.	• Dose reduction required in patients with severe hepatic impairment. • A list of clinical trials is available: Zanubrutinib

Drug Name	**Dosing Regimen** *The doses listed are for approved indications, from clinical trials or clinical experience for COVID-19.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Janus Kinase Inhibitors					
Baricitinib[25]	**EUA Dose for COVID-19**[26] *For Adults and Children Aged ≥9 Years Based on eGFR:* • ≥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** *For Children Aged 2 to <9 Years Based on eGFR:* • ≥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 heart-related events (e.g., heart attack, 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.	• Baricitinib for the treatment of COVID-19 is available through an FDA EUA. See the EUA 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. • A list of clinical trials is available: Baricitinib **Availability:** • Baricitinib, which has been approved for non-COVID-19 indications, is available commercially and through an EUA for the treatment of hospitalized patients with COVID-19 aged ≥2 years.[26]

Drug Name	Dosing Regimen *The doses listed are for approved indications, from clinical trials or clinical experience for COVID-19.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
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–20 mg PO twice daily for 14 days[27]	• Thrombocytopenia • 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 dose >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 Trial:** • Tofacitinib 10 mg PO twice daily for up to 14 days[28]	• 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 heart-related events (e.g., heart attack, 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

Drug Name	Dosing Regimen *The doses listed are for approved indications, from clinical trials or clinical experience for COVID-19.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Non-SARS-CoV-2 Specific Immunoglobulin					
Non-SARS-CoV-2 Specific Immunoglobulin	• Dose varies based on indication and formulation.	• Allergic reactions, including anaphylaxis • Renal failure • Thrombotic events • Aseptic meningitis syndrome • Hemolysis • TRALI • Transmission of infectious pathogens • AEs may vary by formulation. • AEs may be increased with high dose, 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; CHF = congestive heart failure; CPK = creatine phosphokinase; CrCl = creatinine clearance; CRP = C-reactive protein; CYP = cytochrome P450; 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; IFN = interferon; IL = interleukin; IMV = invasive mechanical ventilation; IV = intravenous; IVIG = intravenous immunoglobulin; IVM = ivermectin; MAOI = monoamine oxidase inhibitor; MERS = Middle East respiratory syndrome; NaCl = sodium chloride; OAT = organic anion transporter; the Panel = the COVID-19 Treatment Guidelines Panel; PE = pulmonary embolism; Peg-IFN = pegylated interferon; P-gp= P-glycoprotein; PK = pharmacokinetic; PO = orally; PPI = proton pump inhibitor; RDV = remdesivir; SAE = serious adverse event; SQ = subcutaneous; TB = tuberculosis; TNF = tumor necrosis factor; TRALI = transfusion-related acute lung injury; ULN = upper limit of normal

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Antithrombotic Therapy in Patients with COVID-19

Last Updated: February 11, 2021

Summary Recommendations

Laboratory Testing

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

Chronic Anticoagulant and Antiplatelet Therapy

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

Venous Thromboembolism Prophylaxis and Screening

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

Hospitalized Children With COVID-19

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

Treatment

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

Special Considerations During Pregnancy and Lactation

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

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

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

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

Association Between COVID-19 and Thromboembolism

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

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

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

There are limited prospective data demonstrating the safety and efficacy of using therapeutic doses of anticoagulants to prevent VTE in patients with COVID-19. A retrospective analysis of 2,773 hospitalized COVID-19 patients from a single center in the United States reported in-hospital mortality in 22.5% of patients who received therapeutic anticoagulation and 22.8% of patients who did not receive anticoagulation. The study further reported that in a subset of 395 mechanically ventilated patients, 29.1% of the patients who received anticoagulation and 62.7% of those who did not receive anticoagulation died. The study had important limitations: it lacked details on patient characteristics, indications for anticoagulant initiation, and descriptions of other therapies that the patients received that may have influenced mortality. In addition, the authors did not discuss the potential impact of survival bias on the study results. For these reasons, the data are not sufficient to influence standard of care, and this study further emphasizes the need for prospective trials to define the risks and potential benefits of therapeutic anticoagulation in patients with COVID-19.[18] Three international trials (Antithrombotic Therapy to Ameliorate Complications of COVID-19 [ATTACC], Therapeutic Anticoagulation; Accelerating COVID-19 Therapeutic Interventions and Vaccines-4 [ACTIV-4], and the Randomized, Embedded, Multi-factorial Adaptive Platform Trial for Community-Acquired Pneumonia [REMAP-CAP]) compared the effectiveness of therapeutic dose anticoagulation and prophylactic dose anticoagulation in reducing the need for organ support over 21 days in moderately ill or critically ill adults hospitalized for COVID-19. The need for organ support was defined as requiring high-flow nasal oxygen, invasive or noninvasive mechanical ventilation, vasopressor therapy, or extracorporeal membrane oxygenation (ECMO). The trials paused enrollment of patients requiring intensive care unit (ICU)-level care after an interim pooled analysis demonstrated futility of therapeutic anticoagulation in improving organ support, and a concern for safety. The results of the interim analysis are available on the ATTACC website. Unblinded data and additional study outcomes, including the occurrence of thrombosis, are expected to be reported soon.[19]

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

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

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

Monitoring Coagulation Markers in Patients With COVID-19

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

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

Managing Antithrombotic Therapy in Patients With COVID-19

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

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

Chronic Anticoagulant or Antiplatelet Therapy

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

Patients with COVID-19 Who Are Managed as Outpatients

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

Hospitalized Patients With COVID-19

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

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

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

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

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

Hospitalized Children With COVID-19

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

Patients With COVID-19 Who Are Discharged from the Hospital

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

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

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

Special Considerations During Pregnancy and Lactation

Because pregnancy is a hypercoagulable state, the risk of thromboembolism is greater in pregnant individuals than in nonpregnant individuals.[34] It is not yet known whether COVID-19 increases this risk. In several cohort studies of pregnant women with COVID-19 in the United States and Europe, VTE was not reported as a complication even among women with severe disease, although the receipt of prophylactic or therapeutic anticoagulation varied across the studies.[35-37] The American College of Obstetricians and Gynecologists (ACOG) advises that, although there are no data for or against thromboprophylaxis in the setting of COVID-19 in pregnancy, VTE prophylaxis can reasonably be considered for pregnant women hospitalized with COVID-19, particularly for those who have severe disease.[38] If there are no contraindications to use, the Society of Maternal Fetal Medicine recommends prophylactic heparin or low molecular weight heparin in critically ill or mechanically ventilated pregnant patients.[39] Several professional societies, including the American Society of Hematology and ACOG, have guidelines that specifically address the management of VTE in the context of pregnancy.[40,41] If delivery is threatened, or if there are other risks for bleeding, the risk of bleeding may outweigh the potential benefit of VTE prophylaxis in pregnancy.

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

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

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

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

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

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Supplements

Last Updated: February 11, 2021

Summary Recommendations
Vitamin C • There 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 = Optional **Rating of Evidence:** I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

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.

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.

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 $\leq$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.

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 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]

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.

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 Certain Concomitant Medications in Patients with COVID-19

Last Updated: August 4, 2021

Summary Recommendations
• Patients with COVID-19 who are receiving concomitant medications (e.g., angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], 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 demonstrated safety and efficacy in patients with COVID-19, except in a clinical trial **(AIII)**.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional **Rating of Evidence:** I = One or more randomized trials 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, are at higher risk of severe illness with COVID-19. These patients are often prescribed medications to treat their underlying medical conditions. It is unclear whether these concomitant medications have a positive or negative impact on the treatment and outcomes of COVID-19.

The following section reviews the available data on the use of certain concomitant medications for comorbid conditions in patients with COVID-19 and discusses the considerations clinicians should be aware of when evaluating a patient's concomitant therapy. When prescribing medications for the treatment of COVID-19, clinicians should always assess the patient's current medications for potential drug interactions and adverse effects. The decision to continue or change a patient's medications should be individualized based on their condition.

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)**. Some of these medications have been evaluated as potential treatments for COVID-19; this section will discuss the available data and any additional considerations that clinicians should be aware of when using these medications.

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

Recommendations

- Patients with COVID-19 who are receiving **angiotensin-converting enzyme (ACE) inhibitors** or **angiotensin receptor blockers (ARBs)** for cardiovascular disease (or other non-COVID-19 indications) **should not discontinue** these medications unless discontinuation is otherwise warranted by their clinical condition **(AIIa)**.
- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of **ACE inhibitors** or **ARBs** for the treatment of COVID-19, except in a clinical trial **(AIII)**.

These recommendations are in accord with a joint statement of the American Heart Association, the Heart Failure Society of America, and the American College of Cardiology.[1]

ACE2 is the cell surface receptor for SARS-CoV-2. It has been hypothesized that using ACE inhibitors or ARBs to modulate ACE2 could suppress or enhance SARS-CoV-2 replication.[2,3] Meta-analyses and an ongoing systematic review have not found an association between the use of ACE inhibitors or ARBs and the likelihood of a positive result on a SARS-CoV-2 test or the severity of COVID-19.[4,5]

In a multicenter, open-label randomized trial, hospitalized patients with COVID-19 (n = 659) who were receiving chronic ACE inhibitor therapy or ARB therapy were randomized to continue or discontinue their therapy for 30 days. Treatment of COVID-19 followed local standards of care, and the use of alternative therapies to replace the discontinued medications was at the discretion of the treating physician. The study did not enroll any patients who required invasive mechanical ventilation or who had hemodynamic instability or multiple organ failure.

Overall, there was no difference between the arms in the primary endpoint of days alive and out of the hospital; the mean number of days alive and out of the hospital was 21.9 days in the discontinuation arm and 22.9 days in the continuation arm (mean ratio 0.95; 95% CI, 0.90–1.01). No differences were observed in the secondary endpoints of the percentages of patients who experienced death, cardiovascular events, or COVID-19 progression. Subgroup analyses identified an interaction between the treatment effect and the subgroup of patients who had more severe COVID-19 (those with oxygen saturation <94%, pulmonary infiltrates >50%, or a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen [PaO_2/FiO_2] <300 mm Hg). There may be a clinical benefit to continuing ACE inhibitor therapy or ARB therapy in these patients. Because of limitations in the available data, it is difficult to interpret these findings in patients with certain comorbid conditions, severe or critical illness, and pre-existing diagnoses of heart failure.[6]

Additional investigations into the role of ACE inhibitors, ARBs, and recombinant human ACE2 in the management of COVID-19 are underway.[1] Please see ClinicalTrials.gov for the latest information.

Corticosteroids

Recommendations

- Patients with COVID-19 who are receiving **inhaled or systemic corticosteroids** for an underlying condition **should not discontinue** these medications unless discontinuation is otherwise warranted by their clinical condition **(AIII)**.
- There is insufficient evidence for the Panel to recommend either for or against the use of inhaled budesonide for the treatment of COVID-19.
- Systemic treatment with dexamethasone or other corticosteroids is recommended for certain populations of patients with COVID-19. See Therapeutic Management of Hospitalized Adults With COVID-19, Corticosteroids, and Special Considerations in Pregnancy for specific recommendations.

Oral corticosteroid therapy prescribed for an underlying medical condition (e.g., primary or secondary adrenal insufficiency, rheumatological diseases) should be continued in patients after the diagnosis of COVID-19.[7] Supplemental or stress-dose steroids may be indicated in individual cases.

Inhaled corticosteroids that are used daily by patients with asthma and chronic obstructive pulmonary disease to control airway inflammation should not be discontinued in patients with COVID-19. A large, retrospective study of adult patients with chronic obstructive pulmonary disease and asthma found that those who were prescribed high doses of inhaled corticosteroids had a higher risk of mortality than those who received other inhaled medications without corticosteroids; however, the study had limitations.[8] In fact, the authors suggested that this association may have been due to differences between the groups in the severity of the underlying disease rather than a harmful effect of the inhaled corticosteroids. For patients with COVID-19 who require nebulized corticosteroids, precautions should be taken to minimize the potential for transmission of SARS-CoV-2 in the home and in health care settings.[9,10] Please see Corticosteroids for a summary of the clinical data on using inhaled corticosteroids to manage COVID-19 in outpatients.

The use of corticosteroids has 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 systemic corticosteroids slow SARS-CoV-2 clearance, especially when they are administered earlier in the course of infection.[14-18] There is insufficient evidence to identify a relationship between inhaled corticosteroid use and the speed of viral clearance.

HMG-CoA Reductase Inhibitors (Statins)

Recommendations

- Patients with COVID-19 who are receiving **statin therapy** for an underlying condition **should not discontinue** these medications unless discontinuation is otherwise warranted by their clinical condition **(AIII)**.
- The Panel **recommends against** the use of **statins** for the treatment of COVID-19, except in a clinical trial **(AIII)**.

HMG-CoA reductase inhibitors, or statins, affect ACE2 as part of their function in reducing endothelial dysfunction. It has been proposed that these agents may have a potential role in managing patients with severe COVID-19.[19]

A large observational study in China found that hospitalized patients with COVID-19 who received statins had a lower risk of all-cause mortality than patients who did not receive statins (aHR 0.63; 95% CI, 0.48–0.84; $P = 0.001$).[20] In contrast, a retrospective, multicenter study of critically ill patients with COVID-19 in Italy found no association between the long-term use of statins and mortality (aHR 0.98; 95% CI, 0.81–1.20; $P = 0.87$).[21] Similarly, recent receipt of statin therapy was not associated with a higher mortality risk (aHR 0.96; 95% CI, 0.78–1.18) or the severity of disease (aHR 1.16; 95% CI, 0.95–1.41) in a national cohort study of 4,842 patients with COVID-19 in Denmark.[22]

More data are needed to clarify the impact of statin therapy on COVID-19. Clinical trials that are evaluating the therapeutic impact of statins as an adjunctive therapy for COVID-19 are currently underway. Please see ClinicalTrials.gov for the latest information.

Nonsteroidal Anti-Inflammatory Drugs

Recommendations

- Patients with COVID-19 who are receiving **nonsteroidal anti-inflammatory drugs (NSAIDs)** for an underlying medical condition **should not discontinue** therapy unless discontinuation is otherwise warranted by their clinical condition **(AIII)**.
- Strategies for using **antipyretic therapy** (e.g., acetaminophen, NSAIDs) in patients with COVID-19 should remain similar to the approaches used in other patients **(AIII)**.

In March 2020, news agencies promoted reports that anti-inflammatory drugs may worsen COVID-19. It has been proposed that NSAIDs can increase the expression of ACE2[2] and inhibit antibody production.[23] Shortly after these reports, the Food and Drug Administration stated that there is no evidence linking the use of NSAIDs with worsening of COVID-19 and advised patients to use NSAIDs as directed.[24]

In a national cohort study of patients who tested positive for SARS-CoV-2 infection in Denmark, no association was found between a history of NSAID use and the need for hospitalization, the risk of mortality, or the severity of illness.[25]

Acid-Suppressive Therapy

Recommendations

- Patients with COVID-19 who are receiving **acid-suppressive therapy** for an underlying condition **should not discontinue** these medications unless discontinuation is otherwise warranted by their clinical condition **(AIII)**.
- The Panel **recommends against** the use of **famotidine** for the treatment of COVID-19, except in a clinical trial **(AIII)**.

Acid-suppressive therapies, such as proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs), increase gastric pH. Low gastric pH is proposed to be a protective mechanism against infection with viruses that can enter the body through the gastrointestinal tract (e.g., enteric viruses, SARS-CoV).[26] Observational studies that have evaluated the relationship between the use of acid-suppressive therapy and the acquisition of SARS-CoV-2 or COVID-19 disease severity have produced mixed results.

A propensity-matched cohort study in South Korea observed that current PPI use was not associated with a higher risk of testing positive for SARS-CoV-2, but it was associated with a higher risk of severe illness.[27] An online survey conducted in the United States identified no association between the use of H2RAs and the risk of SARS-CoV-2 infection, while PPI therapy was associated with higher odds of receiving a diagnosis of SARS-CoV-2 infection, especially in those who received twice-daily doses of PPIs.[26] However, these studies had the inherent limitations of observational studies and studies that rely on surveys, and they likely had multiple confounding factors.

The impact of the H2RA famotidine on COVID-19 outcomes has been evaluated in observational studies. In a retrospective study of 878 hospitalized patients with COVID-19, the patients who received famotidine (n = 83) had lower odds of death than those who did not.[28] In another retrospective study of 84 patients who received famotidine and a matched comparator group of 420 patients who did not, the use of famotidine was associated with a reduction in the composite outcome of death or intubation.[29] Only a small proportion of the patients enrolled in these studies received famotidine, and it is unclear what the indications for famotidine therapy were or whether there were other confounding factors. These limitations make it difficult to draw conclusions about the efficacy of using famotidine to treat patients with COVID-19.

Results from ongoing clinical trials will provide more insights into the role of famotidine in the treatment of COVID-19. Please see ClinicalTrials.gov for the latest information.

In patients with COVID-19 who require PPI therapy, the American College of Gastroenterology suggests using the lowest effective dose of the PPI.[30]

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COVID-19 and Special Populations

Last Updated: October 9, 2020

Key Considerations
There is current guidance from the Centers for Disease Control and Prevention (CDC), the American College of Obstetricians and Gynecologists (ACOG), and the Society for Maternal-Fetal Medicine (SMFM) on the management of pregnant patients with COVID-19.[1-4] This section of the COVID-19 Treatment Guidelines complements that guidance. Below are key considerations regarding the management of COVID-19 in pregnancy. • Pregnant women should be counseled about the potential for severe disease from SARS-CoV-2 infection and the recommended measures to take to protect themselves and their families from infection. • If hospitalization for COVID-19 is indicated in a pregnant woman, care should be provided in a facility that can conduct maternal and fetal monitoring, when appropriate. • Management of COVID-19 in the pregnant patient should include: • Fetal and uterine contraction monitoring, when appropriate, based on gestational age   • Individualized delivery planning   • A multispecialty, team-based approach that may include consultation with obstetric, maternal-fetal medicine, infectious disease, pulmonary and critical care, and pediatric specialists, as appropriate • The COVID-19 Treatment Guidelines Panel (the Panel) recommends that potentially effective treatment for COVID-19 should not be withheld from pregnant women because of theoretical concerns related to the safety of therapeutic agents in pregnancy **(AIII)**. • Decisions regarding the use of drugs approved for other indications or investigational drugs for the treatment of COVID-19 in pregnant patients must be made with shared decision-making between the patient and the clinical team, considering the safety of the medication for the pregnant woman and the fetus and the severity of maternal disease. For detailed guidance on the use of COVID-19 therapeutic agents in pregnancy, please refer to the pregnancy considerations subsection of each individual section of the Guidelines.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional **Rating of Evidence:** I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

To date, most of the data generated about the epidemiology, clinical course, prevention, and treatment of COVID-19 have come from studies of nonpregnant adults. More information is urgently needed regarding COVID-19 in other patient populations, such as in children, pregnant individuals, and other populations as outlined in the following sections of the Guidelines.

Although children with COVID-19 may have less severe disease overall than adults with COVID-19, the recently described multisystem inflammatory syndrome in children (MIS-C) requires further study. Data are also emerging on the clinical course of COVID-19 in pregnant patients, pregnancy outcomes in the setting of COVID-19, and vertical transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). There are special considerations for transplant recipients, patients with cancer, persons with HIV, and patients with other immunocompromising conditions, as some of these patients may be at increased risk of serious complications as a result of COVID-19.

The following sections review the available data on COVID-19 in some of these populations and discuss the specific considerations that clinicians should take into account for the prevention and treatment of SARS-CoV-2 infections in these populations.

Special Considerations in Pregnancy

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

Epidemiology of COVID-19 in Pregnancy

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 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-CoV2 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 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.

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: April 21, 2021

Summary Recommendations
• 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 nonwhite 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, invasive mechanical ventilation, or extracorporeal membrane oxygenation **(BIII)**. • There is insufficient 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 one 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.   • Consultation with a multidisciplinary team is recommended when considering and managing immunomodulating therapy for children with MIS-C **(AIII)**. Intravenous immunoglobulin and/or corticosteroids are generally used as first-line therapy, although interleukin-1 antagonists have been used for refractory cases. The optimal choice and combination of immunomodulating therapies have not been definitively established.

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

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

Epidemiology

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 unit on 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 neurologic and developmental disorders.

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 of asthma with severe disease is not clearly defined.[7,8] Congenital heart disease may be associated with 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 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 Mothers 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 two 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 and 12% had suspected nosocomially acquired infection.[29] Specific guidance on the diagnosis and management of COVID-19 in neonates born to mothers with known or suspected SARS-CoV-2 infection is provided by CDC.

Treatment Considerations

There are no results available from clinical trials evaluating treatment 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 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 detailed 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 condition 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 detailed information). The safety and effectiveness of dexamethasone or other corticosteroids for COVID-19 treatment have not been sufficiently evaluated in pediatric patients and 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, invasive 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 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 and casirivimab plus imdevimab 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 monoclonal antibodies 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, bamlanivimab plus etesevimab or casirivimab plus imdevimab 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 efficacy or safety in children or adolescents, limited data with which to identify children at the highest risk of severe COVID-19, as well as 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 monoclonal antibodies in hospitalized children for COVID-19. Emerging data regarding the prevalence and clinical significance of SARS-CoV-2 variants, and the efficacy of monoclonal antibodies against variants, may inform the choice of specific anti-SARS-CoV-2 monoclonal antibody therapy 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 detailed 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, invasive 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 detailed information).

Tocilizumab

Data on tocilizumab use 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 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 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 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 use of these drugs in children and refer to Table 2e and Table 4e 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 PIMS-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 nonwhite, 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 requiring hospitalization with multisystem (i.e., more than two) 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; 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 one or more of the following: an elevated C-reactive protein, erythrocyte sedimentation

rate, fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase, interleukin (IL)-6, or neutrophils, or reduced lymphocytes or albumin levels

Distinguishing MIS-C from other febrile illnesses in the community setting remains challenging, but 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 those 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, as well as coronary artery dilations, and rarely, coronary artery aneurysms. 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 IL-10) between MIS-C and acute COVID-19 in children.[56-58]

Management

Currently, there are only observational data available to guide treatment for MIS-C. Supportive care remains the mainstay of therapy. There is currently insufficient evidence for the Panel to recommend either for or against any specific therapeutic strategy for the management of MIS-C. MIS-C management decisions should involve a multidisciplinary team of pediatric specialists including experts in intensive care, infectious diseases, cardiology, hematology, and rheumatology. Although no clinical trial data are available, many centers have described the use of immunomodulatory therapy (e.g., intravenous immune globulin [IVIG], corticosteroids, IL-1 and IL-6 inhibitors). The American College of Rheumatology has outlined initial diagnostic and treatment considerations for MIS-C, recommending IVIG and/or corticosteroids as first-tier therapies and other biologic agents as second-line options.[48,49,59] An observational study from Europe used propensity matching to compare short-term outcomes in children with MIS-C who were treated initially with IVIG alone or IVIG and methylprednisolone. They observed a lower risk of treatment failure (defined as persistence of fever), more rapid improvement in hemodynamic support, less severe left ventricular dysfunction, and shorter ICU stays among children initially treated with the combination therapy.[60] These findings must be confirmed with additional prospective studies. The role of antiviral therapy in MIS-C is not clear, therefore the use of remdesivir should be reserved for patients who have features of acute COVID-19.

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Special Considerations in Adults and Children With Cancer

Last Updated: October 19, 2021

Summary Recommendations
• 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 or patients who are receiving treatment for cancer **(AIII)**. • Patients who are receiving active cancer therapy may have suboptimal responses to the current two-dose vaccine series. Because of this, the Centers for Disease Control and Prevention recommends a third dose of an mRNA vaccine for these patients. See the text below for additional information on the criteria for receiving a third dose and the appropriate timing for COVID-19 vaccination in these patients. • 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 for treatment or as post-exposure prophylaxis (PEP). • The Panel recommends performing molecular diagnostic testing for SARS-CoV-2 in patients with cancer who develop signs and symptoms that suggest COVID-19 **(AIII)** and in asymptomatic patients prior to procedures that require anesthesia and before initiating cytotoxic chemotherapy and long-acting biologic therapy **(BIII)**. • The recommendations for treating COVID-19 in patients with cancer are the same as those for the general population **(AIII)**. See 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 drug-drug interactions and overlapping toxicities between drugs that are used to treat COVID-19 and cancer-directed therapies, prophylactic antimicrobials, corticosteroids, and other medications **(AIII)**. • Clinicians who are treating COVID-19 in patients with cancer should consult a hematologist or oncologist before adjusting cancer-directed medications **(AIII)**. • Decisions about administering cancer-directed therapy during SARS-CoV-2 infection should be made on a case-by-case basis; clinicians should consider the indication for chemotherapy, the goals of care, and the patient's history of tolerance to the treatment **(BIII)**.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional **Rating of Evidence:** I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

People who are being treated for cancer may be at increased risk of severe COVID-19, and 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 were at lower risk of death from COVID-19 than those who were receiving active treatment.[6] It is unclear whether cancer survivors are at increased risk for severe COVID-19 and its complications compared to people without a history of cancer.

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

- National Comprehensive Cancer Network (NCCN)
- American Society of Hematology (ASH)

- 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.

Vaccination for COVID-19 in Patients With Cancer

The clinical trials that evaluated the COVID-19 vaccines that have received Emergency Use Authorizations and/or approval from the Food and Drug Administration (FDA) excluded severely immunocompromised patients. The Advisory Committee on Immunization Practices notes that the authorized COVID-19 vaccines 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 or patients who are receiving treatment for cancer **(AIII)**. The Centers for Disease Control and Prevention (CDC) recommends a third dose of an mRNA vaccine for patients who are receiving active cancer therapy; this third dose should be administered at least 28 days after the completion of the initial two-dose mRNA COVID-19 vaccine series.[8] ASH and NCCN have provided additional recommendations for administering a third vaccine dose in patients with cancer based on the patient's tumor type and therapy.[9,10]

The mRNA vaccines contain polyethylene glycol (PEG), and the Johnson & Johnson (J&J)/Janssen vaccine contains polysorbate. In patients who experience a severe anaphylactic reaction 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.[11-13]

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 COVID-19 at least 2 weeks before starting chemotherapy.[9,14]
- 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.[15]
- Hematopoietic stem cell and chimeric antigen receptor T cell recipients can be offered COVID-19 vaccination starting at least 3 months after therapy.[14]

It is unknown whether the immune response to COVID-19 vaccination can increase the risk of graft-versus-host disease. Studies of patients who received immune checkpoint inhibitors did not report immune-related adverse events in these patients after vaccination.[16,17]

Decreased immunologic responses to COVID-19 vaccination have been reported in patients who were receiving treatment for solid tumors and hematologic malignancies.[18,19] 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).[19] In comparison, approximately 80% to 95% of patients with solid tumors showed immunologic responses.[18,20,21] Currently, it is not known how a third dose of an mRNA vaccine affects response rates in patients with cancer.

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 (mAbs) as post-exposure prophylaxis (PEP).

Vaccination of household members, close contacts, and health care providers who provide care for immunocompromised patients is imperative to protect these patients from infection. All close contacts are strongly encouraged to get vaccinated.

Testing for SARS-CoV-2 in Patients With Cancer

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

Patients with cancer who are receiving chemotherapy are at risk of developing neutropenia. The NCCN Guidelines for Hematopoietic Growth Factors categorizes cancer treatment regimens based on the patient's risk of developing neutropenia.[22] A retrospective study suggests that patients with cancer and neutropenia have a higher mortality rate if they develop COVID-19.[23] 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.[24,25] Because of this, the Panel recommends performing molecular diagnostic testing for SARS-CoV-2 prior to procedures that require anesthesia and before initiating cytotoxic chemotherapy and long-acting biologic therapy **(BIII)**.

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. CDC has published a framework to help clinicians decide whether a patient should receive in-person or virtual care during the COVID-19 pandemic; this framework accounts for factors such as the potential harm of delayed care and the degree of SARS-CoV-2 transmission in a patient's community.[26] Telemedicine may improve access to providers for medically or socially vulnerable populations, but it could worsen disparities if these populations have limited access to technology. Nosocomial transmission of SARS-CoV-2 to patients and health care workers has been reported.[27-29] Principles of physical distancing and prevention strategies, including masking patients and health care workers and practicing hand hygiene, apply to all in-person interactions.[30]

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, treatment delays should be avoided for curable cancers that have been shown to have worse outcomes when treatment is delayed (e.g., pediatric acute lymphoblastic leukemia).
- When deciding between equally effective treatment regimens, regimens that can be administered orally or those that require fewer infusions are preferred.[31]
- 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.[32]

- 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.[33]
- 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.[34] A retrospective study from Italy evaluated the incidence of SARS-CoV-2 infection in patients with prostate cancer and found that 114 of 37,161 patients (0.3%) who were treated with therapies other than androgen deprivation therapy became infected, compared to 4 of 5,273 patients (0.08%) who were treated with androgen deprivation therapy (OR 4.05; 95% CI, 1.55–10.59).[35] A small cohort study of patients from Finland with prostate cancer did not find an association between androgen deprivation and the incidence of SARS-CoV-2 infection.[36] The viral spike proteins that SARS-CoV-2 uses to enter cells are primed by transmembrane serine protease 2 (TMPRSS2), an androgen-regulated gene. Whether androgen deprivation therapy protects against SARS-CoV-2 infection requires further investigation in larger cohorts or clinical trials.[35]
- Radiation therapy guidelines suggest increasing the dose per fraction and reducing the number of daily treatments to minimize the number of hospital visits.[37,38]

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.[39] In patients with cancer, stricter transfusion thresholds for blood products (e.g., red blood cells, platelets) in asymptomatic patients should be considered.[8] At this time, there is no evidence that COVID-19 can be transmitted through blood products.[40,41]

Febrile Neutropenia

Patients with cancer and febrile neutropenia should undergo molecular diagnostic testing for SARS-CoV-2 and evaluation for other infectious agents; they should also be given empiric antibiotics, as outlined in the NCCN Guidelines.[42] 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.[42] 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.[43,44]

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 serious COVID-19, and they may be eligible to receive anti-SARS-CoV-2 mAbs as treatment if they develop mild to moderate COVID-19.

Dexamethasone treatment has been associated with a lower mortality rate in patients with COVID-19 who require supplemental oxygen or invasive mechanical ventilation.[45] 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.

The NCCN recommends against using G-CSF and granulocyte-macrophage colony-stimulating factor in patients with cancer and acute SARS-CoV-2 infection who do not have bacterial or fungal infections to avoid the hypothetical risk of increasing inflammatory cytokine levels and pulmonary inflammation.[46,47] Secondary infections (e.g., invasive pulmonary aspergillosis) have been reported in critically ill patients with COVID-19.[48,49]

Decisions about administering cancer-directed therapy to patients with acute COVID-19 and those who are recovering from COVID-19 should be made on a case-by-case basis; clinicians should consider the indication for chemotherapy, the goals of care, and the patient's history of tolerance to the treatment **(BIII)**. The optimal duration of time between resolution of infection and initiating or restarting cancer-directed therapy is unclear. Withholding treatment until COVID-19 symptoms have resolved is recommended, if possible. Prolonged viral shedding (detection of SARS-CoV-2 by molecular testing) may occur in 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 drug-drug interactions and overlapping toxicities between drugs that are used to treat COVID-19 and cancer-directed therapies, prophylactic antimicrobials, corticosteroids, and other medications **(AIII)**.

Several antineoplastic medications may interact with therapies that are being investigated for COVID-19.[50,51] For example, tocilizumab can interact with vincristine and doxorubicin. Any COVID-19 therapy that may cause QT prolongation must be used with caution in patients who are being treated with venetoclax, gilteritinib, or tyrosine kinase inhibitor therapy (e.g., nilotinib). 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 cytochrome P450 (CYP) 3A4 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.[52-54] 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.[55] Two publications include guidance for managing specific malignancies, guidance for supportive care, and a summary of web links from expert groups that are relevant to the care of pediatric oncology patients during the COVID-19 pandemic.[55,56]

Special considerations for using antivirals in immunocompromised children, including those with malignancy, are available in a multicenter guidance statement.[57]

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

Last Updated: October 19, 2021

Summary Recommendations

Vaccination for COVID-19

- 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 recipients, the COVID-19 Treatment Guidelines Panel (the Panel) recommends COVID-19 vaccination for potential transplant and cellular immunotherapy candidates, potential donors, and recipients **(AIII)**. See the text below for information on the appropriate timing for COVID-19 vaccination in these patients.
- A third dose of an mRNA vaccine (given at least 4 weeks after the second dose) is currently recommended by the Centers for Disease Control and Prevention for solid organ transplant (SOT) recipients who are taking immunosuppressive medications and hematopoietic stem cell transplant (HCT) recipients who are within 2 years of transplantation or who are taking immunosuppressive medications.

Potential Transplant and Cellular Immunotherapy Candidates

- The Panel recommends diagnostic molecular testing for SARS-CoV-2 for all potential SOT, 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 SOT, HCT, or cellular immunotherapy recipients when performing diagnostic molecular testing for SARS-CoV-2 in these patients **(AIII)**.
- If SARS-CoV-2 is detected or if infection is strongly suspected, transplantation should be deferred, if possible **(BIII)**.
- 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)**.
- Additionally, many transplant candidates are at high risk of progressing to serious COVID-19, and they may be eligible to receive anti-SARS-CoV-2 monoclonal antibodies (mAbs) for treatment or post-exposure prophylaxis (PEP).

Potential Transplant Donors

- The Panel recommends assessing all potential SOT and HCT donors for signs and symptoms that are associated with COVID-19 according to guidance from medical professional organizations **(AIII)**.
  - The Panel recommends performing diagnostic molecular testing for SARS-CoV-2 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 for more information.
- Immunocompromised patients with mild to moderate COVID-19 are at high risk of progressing to serious disease, and they may be eligible to receive anti-SARS-CoV-2 mAbs for treatment or PEP.
- The Panel recommends that clinicians who are treating COVID-19 in transplant and cellular immunotherapy patients consult with a transplant specialist before adjusting immunosuppressive medications **(AIII)**.
- When treating COVID-19, clinicians should pay careful attention to potential drug-drug interactions and overlapping toxicities with immunosuppressants, prophylactic antimicrobials, and other medications **(AIII)**.

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

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

Introduction

Treating COVID-19 in solid organ transplant (SOT), hematopoietic stem cell transplant (HCT), and cellular immunotherapy recipients can be challenging due to the presence of coexisting medical conditions, transplant-related cytopenias, and the need for chronic immunosuppressive therapy to prevent graft rejection and graft-versus-host disease. Transplant recipients may also have increased 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 the intensity of the immunosuppressive effect of the agent, as well as by specific combinations of immunosuppressive agents. Some transplant recipients have medical comorbidities that have been associated with more severe cases of COVID-19 and a greater risk of mortality, which makes the impact of transplantation on disease severity difficult to assess.

The International Society for Heart and Lung Transplantation, the American Society of Transplantation, 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 SOT, 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 for more information. The medications that are used to treat COVID-19 may present different risks and benefits to transplant patients and nontransplant patients.

Vaccination for COVID-19 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 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] Compared to healthy vaccine recipients, SOT recipients have a reduced antibody response following a primary two-dose vaccine series of mRNA vaccines.[5-7] Among those who had no detectable antibody response to the initial two-dose vaccine series, 33% to 50% of patients developed an antibody response to an additional mRNA vaccine dose.[8,9]

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 recipients, the COVID-19 Treatment Guidelines Panel (the Panel) recommends COVID-19 vaccination for potential transplant and cellular immunotherapy candidates, potential donors, and recipients **(AIII)**. Currently, the Centers for Disease Control and Prevention recommends administering an additional dose of vaccine to moderately to severely immunocompromised people at least 28 days after a second dose of an mRNA vaccine.[10] This includes people who have:

- Received an SOT and are taking immunosuppressive medications
- Received an HCT within the last 2 years or who are taking immunosuppressive medications

When determining the timing of COVID-19 vaccination in SOT, HCT, and cellular immunotherapy recipients, clinicians should consider the following factors:

- Ideally, SOT candidates should receive COVID-19 vaccines while they are awaiting transplant.
- In general, vaccination should be completed at least 2 weeks prior to SOT or started 1 month after SOT.
- In certain situations, it may be appropriate to delay vaccination until 3 months after SOT, such as when T cell- or B cell-ablative therapy (with antithymocyte globulin or rituximab) is used at the time of transplant.[11]
- At this time, reducing the dose of immunosuppressants and holding 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.[12-14] 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 continue wearing a mask, maintain a distance of 6 feet from others, and avoid crowds and poorly ventilated spaces).[15]

It remains unclear whether the immune responses to COVID-19 vaccines can increase the risk of graft-versus-host disease or other immune-related complications.[14,16] Outside of a clinical study, antibody testing **is not recommended** to assess immunity to SARS-CoV-2 following COVID-19 vaccination in transplant patients. It is currently unknown whether revaccination offers a clinical benefit for people who received COVID-19 vaccines during treatment with immunosuppressive drugs.

Vaccination of household members, close contacts, and health care providers who provide care for immunocompromised patients is imperative to protect immunocompromised patients from infection. All close contacts are strongly encouraged to get vaccinated as soon as possible.

Post-Exposure Prophylaxis for Transplant and Cellular Immunotherapy Recipients

The Food and Drug Administration (FDA) expanded the Emergency Use Authorization (EUA) indication for the anti-SARS-CoV-2 monoclonal antibodies (mAbs) bamlanivimab plus etesevimab and casirivimab plus imdevimab to allow them to be used as post-exposure prophylaxis (PEP) for selected individuals who are at high risk for disease progression. This includes immunocompromised individuals who are not expected to mount an adequate immune response to vaccination. See Prevention of SARS-CoV-2 Infection for more information.

Assessment of 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.

Assessment of Transplant and Cellular Immunotherapy Candidates

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

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

Assessment of Donors

Living solid organ donors should be counseled on strategies to prevent infection and monitored for exposures and symptoms in the 14 days prior to a scheduled transplant.[17] Living donors should undergo respiratory tract SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) testing 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 **(BIII)**.

Lower respiratory sampling for COVID-19 testing is required for potential lung transplant donors by the United Network for Organ Sharing.[18] 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 group gatherings during the 28 days prior to donation.[19] Recommendations for screening for HCT donors are outlined in the ASTCT and EBMT guidelines.

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

If SARS-CoV-2 is detected or if infection is strongly suspected in a potential SOT candidate, transplant should be deferred, if possible **(BIII)**. The optimal disease-free interval before transplantation is not known. The risks of viral transmission should be balanced against the risks to the candidate, such as progression of the underlying disease and risk of mortality if the candidate does not receive the transplant. This decision should be continually reassessed as conditions evolve. Donors for SOT who test positive for SARS-CoV-2 are medically ineligible for donation.[20] For HCT and cellular immunotherapy candidates, current guidelines recommend deferring transplants or immunotherapy procedures, including peripheral blood stem cell mobilization, bone marrow harvest, T cell collection, and conditioning/lymphodepletion in recipients who test positive for SARS-CoV-2 or who have clinical symptoms that are consistent with infection. Final decisions should be made on a case-by-case basis while weighing the risks of delaying or altering therapy for the underlying disease.

Transplant Recipients With COVID-19

SOT recipients who are receiving immunosuppressive therapy should be considered to be at increased risk for severe COVID-19.[21,22] A national survey of 88 U.S. transplant centers conducted between March 24 and 31, 2020, reported that 148 SOT recipients received a diagnosis of 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).[23] COVID-19 was mild in 54% of recipients, moderate in 21% of recipients, and 25% of recipients were critically ill. Management strategies varied widely across the transplant centers, including different ways of modifying immunosuppressive therapy and the use of different investigational therapies to treat COVID-19. Initial reports of transplant recipients who were hospitalized with COVID-19 suggest mortality rates of up to 28%.[24-28]

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 SOT 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.[21]

There are limited data on the incidence and clinical characteristics of SARS-CoV-2 infection in HCT and cellular immunotherapy recipients. 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.[29] 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.[30] 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 SOT and HCT recipients; this can have implications for preventing infection and for the timing of therapeutic interventions.[31]

Treatment of COVID-19 in Transplant Recipients

Currently, the antiviral agent remdesivir is the only drug that is approved by the FDA for the treatment of COVID-19. Outpatient transplant recipients who are immunosuppressed or who have certain underlying comorbidities are candidates for the anti-SARS-CoV-2 mAbs that are available through EUAs (see Anti-SARS-CoV-2 Monoclonal Antibodies). Transplant recipients who are hospitalized for reasons other than COVID-19 are also eligible to receive mAb therapy. Transplant recipients who are hospitalized with mild to moderate COVID-19 may be considered for anti-SARS-CoV-2 mAbs that are available through expanded access programs.

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 patients with COVID-19 who were mechanically ventilated or who required supplemental oxygen.[32] 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 Interleukin-6 Inhibitors).[33-35] The risks and benefits of using dexamethasone in combination with tocilizumab or baricitinib in transplant recipients with COVID-19 who are receiving immunosuppressive therapy are unknown. Because dexamethasone, tocilizumab, and baricitinib are immunosuppressive agents, patients who receive these medications should be closely monitored for secondary infections.

The Panel's recommendations for the use of remdesivir, dexamethasone, tocilizumab, and baricitinib in patients with COVID-19 can be found in Therapeutic Management of Hospitalized Adults With COVID-19.

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

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 (e.g., corticosteroids, mycophenolate, and calcineurin inhibitors such as tacrolimus and cyclosporine), antimicrobials that are used to prevent opportunistic infections, and other medications. Dose modifications may be necessary for drugs that are used to treat COVID-19 in transplant recipients with pre-existing organ dysfunction. Adjustments to the immunosuppressive regimen should be individualized based on disease severity, the specific immunosuppressants used, the type of transplant, the time since transplantation, the drug concentration, and the risk of graft rejection.[25] Clinicians who are treating COVID-19 in transplant patients should consult a transplant specialist before adjusting immunosuppressive medication **(AIII)**.

Certain therapeutics (e.g., remdesivir, tocilizumab, baricitinib) are associated with elevated levels of transaminases. For liver transplant recipients, the American Association for the Study of Liver Diseases does not consider abnormal liver biochemistries a contraindication to using remdesivir.[36] Close monitoring of liver biochemistries is warranted in patients with COVID-19, especially when they are receiving agents with a known risk of hepatotoxicity.

Calcineurin inhibitors, which are commonly used to prevent allograft rejection, have a narrow therapeutic index. Medications that inhibit or induce cytochrome P450 (CYP) enzymes or P-glycoprotein may put patients who receive calcineurin inhibitors at risk of clinically significant drug-drug interactions, increasing the need for therapeutic drug monitoring and the need to assess for signs of toxicity or rejection.[37] Among the drugs that are commonly used to treat COVID-19, dexamethasone is a moderate inducer of CYP3A4, and interleukin-6 inhibitors may lead to increased metabolism of CYP substrates. Close monitoring of serum concentration of calcineurin inhibitors should be considered when these drugs are used.

Additional details about the adverse effects and drug interactions of antiviral medications and immune-based therapy for COVID-19 are noted in Tables 2e, 3c, and 4e.

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Special Considerations in People With HIV

Last Updated: October 19, 2021

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 two-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 HIV who have recently been in close contact with a person with SARS-CoV-2 infection are eligible to receive anti-SARS-CoV-2 monoclonal antibodies (mAbs) as post-exposure prophylaxis (PEP); however, in situations where there are logistical or supply constraints for administering mAbs, priority should be given to those with advanced HIV **(AIII)**. See Prevention of SARS-CoV-2 Infection for the specific indications for PEP.

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 are eligible to receive anti-SARS-CoV-2 mAbs for treatment; however, in situations where there are logistical or supply constraints for administering mAbs, priority should be given to those with advanced HIV **(AIII)**.
- 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 antiretroviral therapy (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)**.
- 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 = Optional

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

Introduction

Approximately 1.2 million 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.

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 managing 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 Interim Guidance for COVID-19 and Persons 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 a 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.[3-10] For example, the Veterans Aging Cohort Study compared the clinical outcomes for 253 veterans with HIV and COVID-19 and the outcomes for a matched comparator arm of 504 veterans without HIV who developed COVID-19. More than 95% of the participants in this study were male. In this comparison, no differences were found between the outcomes for patients with HIV and those who did not have HIV.[11]

In contrast, worse outcomes for patients with HIV and COVID-19, including increased COVID-19 mortality rates, have been reported by subsequent 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, invasive 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]

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 two 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, the safety and efficacy of these vaccines in people with HIV have not been fully reported. 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 two 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. Guidance for using these vaccines, including guidance for people with HIV, is available through the Advisory Committee on Immunization Practices. A patient's HIV status should be kept confidential when administering a vaccine.

People with HIV who have recently been in close contact with a person with SARS-CoV-2 infection are eligible to receive anti-SARS-CoV-2 monoclonal antibodies (mAbs) as post-exposure prophylaxis (PEP); however, in situations where there are logistical or supply constraints for administering mAbs, priority should be given to those with advanced HIV **(AIII)**. See Prevention of SARS-CoV-2 Infection for the specific indications for PEP.

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) 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 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, tobacco use disorder, 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.[3-10,31,32] 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 are eligible to receive anti-SARS-CoV-2 mAbs for treatment; however, in situations where there are logistical or supply constraints for administering mAbs, priority should be given to those with advanced HIV **(AIII)**. See Prevention of SARS-CoV-2 Infection for more information. In hospitalized patients, the appropriate treatment strategy depends on disease severity (see Therapeutic Management of Hospitalized Adults With COVID-19).

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)**. 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 it 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 are being studied for the prevention and treatment of COVID-19, no agents have been shown to be effective.

People with HIV should be offered the opportunity to participate in clinical trials of vaccines and potential treatments for COVID-19. A variety of immunomodulatory therapies are prescribed empirically or administered as part of a clinical trial to treat severe COVID-19. 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 SARS-CoV-2/HIV Coinfection

Below are some general considerations regarding the management of HIV in people with SARS-CoV-2/HIV coinfection.

- 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 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 Clinical Consultation Center, Monday through Friday, 9 am to 8 pm EST.

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Influenza and COVID-19

Last Updated: October 22, 2020

Summary Recommendations
Influenza Vaccination • Although data are lacking on influenza vaccination for persons with COVID-19, on the basis of practice for other acute respiratory infections, the Panel recommends that persons with COVID-19 should receive an inactivated influenza vaccine **(BIII)**. The Centers for Disease Control and Prevention (CDC) has provided guidance on the timing of influenza vaccination for inpatients and outpatients with COVID-19 (see Interim Guidance for Routine and Influenza Immunization Services During the COVID-19 Pandemic). **Diagnosis of Influenza and COVID-19 When Influenza Viruses and SARS-CoV-2 Are Cocirculating** • Only testing can distinguish between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and influenza virus infections and identify SARS-CoV-2 and influenza virus coinfection. • When SARS-CoV-2 and influenza viruses are cocirculating, the Panel recommends testing for both viruses in all hospitalized patients with acute respiratory illness **(AIII)**. • When SARS-CoV-2 and influenza viruses are cocirculating, the Panel recommends influenza testing in outpatients with acute respiratory illness if the results will change clinical management of the patient **(BIII)**. • Testing for other pathogens should be considered depending on clinical circumstances, especially in patients with influenza in whom bacterial superinfection is a well-recognized complication. • See the CDC Information for Clinicians on Influenza Virus Testing and the Infectious Diseases Society of America (IDSA) Clinical Practice Guidelines for more information. **Antiviral Treatment of Influenza When Influenza Viruses and SARS-CoV-2 Are Cocirculating** • The treatment of influenza is the same in all patients regardless of SARS-CoV-2 coinfection **(AIII)**. • The Panel recommends that hospitalized patients be started on empiric treatment for influenza with oseltamivir as soon as possible without waiting for influenza testing results **(AIIb)**.   • Antiviral treatment of influenza can be stopped when influenza has been ruled out by nucleic acid detection assay in upper respiratory tract specimens for nonintubated patients and in both upper and lower respiratory tract specimens for intubated patients. • For influenza treatment in hospitalized and non-hospitalized patients, see the CDC and IDSA recommendations on antiviral treatment of influenza.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional **Rating of Evidence:** I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

Introduction

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

Influenza Vaccination

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

Clinical Presentation of Influenza Versus COVID-19

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

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

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

Which Patients Should Receive Antiviral Treatment of Influenza?

When SARS-CoV-2 and influenza viruses are cocirculating in the community, patients who require hospitalization and are suspected of having either or both viral infections should receive influenza antiviral treatment with oseltamivir as soon as possible without waiting for influenza testing results **(AIIb)**.[14] Treatment for influenza is the same for all patients regardless of SARS-CoV-2 coinfection **(AIII)**. See the CDC Influenza Antiviral Medications: Summary for Clinicians, including clinical algorithms for antiviral treatment of patients with suspected or confirmed influenza when SARS-CoV-2 and influenza viruses are cocirculating, and the IDSA Clinical Practice Guidelines recommendations on antiviral treatment of influenza.

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

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

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

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

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

Last Updated: October 19, 2021

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Ex Officio Members, U.S. Government Representatives	
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Appendix A, Table 2. COVID-19 Treatment Guidelines Panel Financial Disclosure for Companies Related to COVID-19 Treatment or Diagnostics

Last Updated: October 19, 2021

Reporting Period: April 1, 2020, to March 31, 2021

Panel Member	Financial Disclosure	
	Company	**Relationship**
Judith Aberg, MD	Atea Pharmaceuticals	Research Support
	Emergent BioSolutions	Research Support
	Frontier Technologies	Research Support
	Gilead Sciences	Research Support
	GlaxoSmithKline	Advisory Board, Research Support
	Janssen	Research Support
	Merck & Co.	Advisory Board, Research Support
	Pfizer	Research Support
	Regeneron	Research Support
	ViiV Healthcare	Advisory Board, Research Support
Adaora Adimora, MD, MPH	Merck & Co.	Advisory Board, Consultant, Research Support
Jason Baker, MD, MS	Gilead Sciences	Research Support
	Humanigen	Research Support
Lisa Baumann Kreuziger, MD, MS	3M	Stockholder, Spouse Is Employee
	Versiti	Employee
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	ViiV Healthcare	Advisory Board
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John T. Brooks, MD	None	N/A
Timothy Burgess, MD	None	N/A
Danielle M. Campbell, MPH	Gilead Sciences	Advisory Board
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Craig Coopersmith, MD	None	N/A
Page Crew, PharmD, MPH	None	N/A
Eric Daar, MD	Gilead Sciences	Consultant, Research Support
	Merck & Co.	Consultant, Research Support
	ViiV Healthcare	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
Gregory Eschenauer, PharmD	None	N/A

Panel Member	Financial Disclosure	
	Company	**Relationship**
Laura Evans, MD, MSc	None	N/A
Joseph Francis, MD, MPH	None	N/A
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Rajesh Gandhi, MD	None	N/A
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	Merck & Co.	Advisory Board
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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
Lauren Henderson, MD, MMSc	Adaptive Biotechnologies	Consultant
	Bristol Myers Squibb	Research Support
	Cerecor	Consultant
	Pfizer	External Panel for Grant Reviews
	Sobi	Consultant
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Carl Hinkson, MSRC	None	N/A
Brenna L. Hughes, MD, MSc	Merck & Co.	Advisory Board
Steven Johnson, MD	ViiV Healthcare	Advisory Board
Marla J. Keller, MD	None	N/A
Arthur Kim, MD	None	N/A
Safia Kuriakose, PharmD	None	N/A
H. Clifford Lane, MD	None	N/A
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	Regeneron Pharmaceuticals	Consultant
	Sanofi	Consultant
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Gregory Martin, MD, MSc	Apellis	Data and Safety Monitoring Board Chair/Member
	Beckman Coulter	Consultant
	Genentech	Data and Safety Monitoring Board Chair/Member
	Grifols	Research Grants Review Panel
	Regeneron	Consultant
Henry Masur, MD	None	N/A

Panel Member	Financial Disclosure	
	Company	**Relationship**
Susanna Naggie, MD, MHS	AbbVie	Research Support
	Bristol Myers Squibb	Event Adjudication
	Gilead Sciences	Research Support
	Vir Biotechnology	Advisory Board, Stockholder
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Kanal Singh, MD, MPH	None	N/A
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	Merck & Co.	Research Support
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Alpana A. Waghmare, MD	AlloVir	Research Support
	Ansun BioPharma	Research Support
	Kyorin Pharmaceutical Co.	Advisory Board
Kevin C. Wilson, MD	None	N/A
Jinoos Yazdany, MD, MPH	AstraZeneca	Consultant, Research Support
	Aurinia	Consultant
	Bristol Myers Squibb	Research Support
	Eli Lilly and Company	Consultant
	Gilead Sciences	Research Support
	Pfizer	Consultant
Philip Zachariah, MD, MSc	Merck & Co.	Research Support