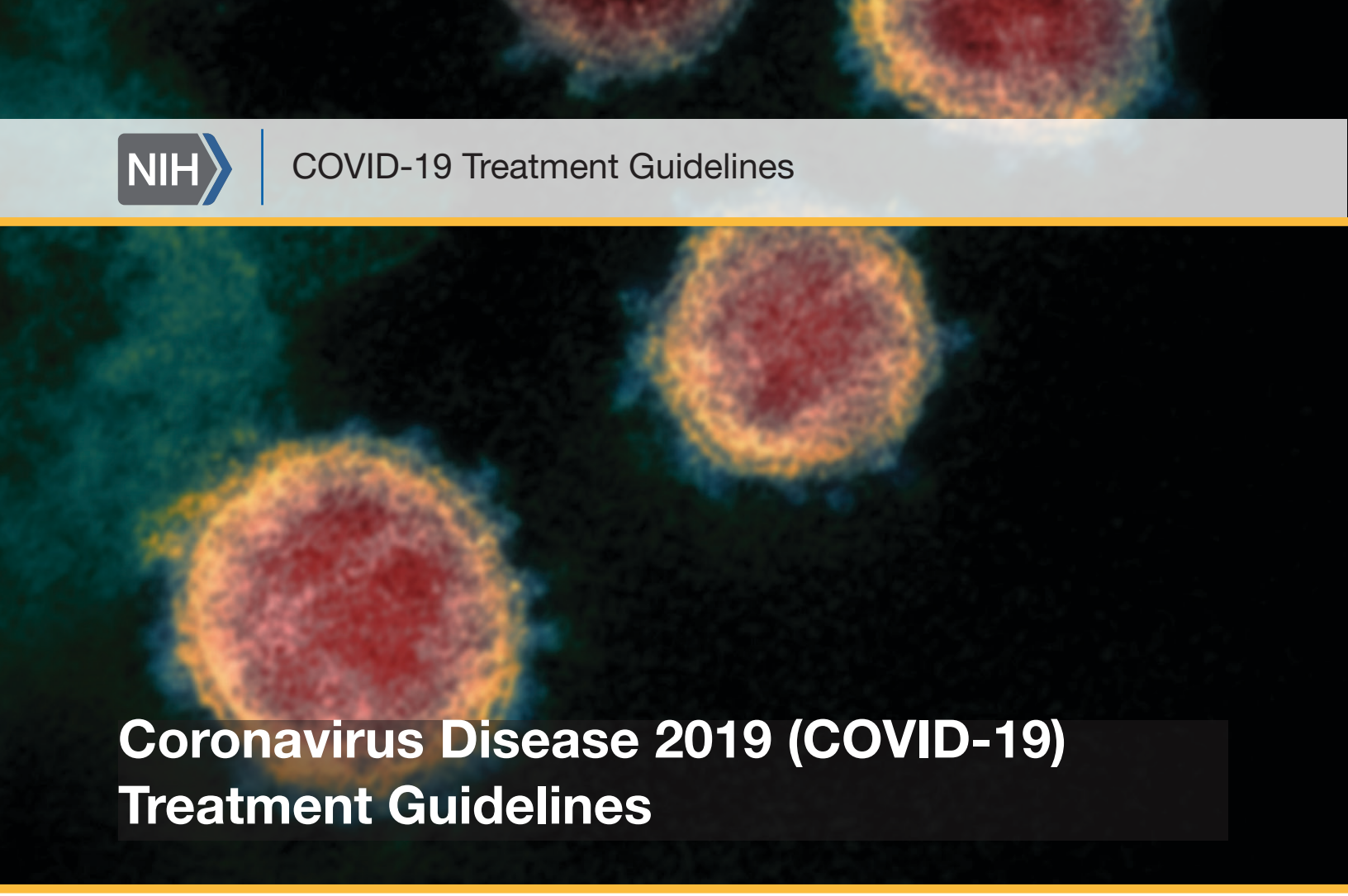

COVID-19 Treatment Guidelines

Coronavirus Disease 2019 (COVID-19) Treatment Guidelines

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How to Cite the COVID-19 Treatment Guidelines:

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

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What's New in the Guidelines

Last Updated: January 10, 2023

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

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

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

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

January 10, 2023

The COVID-19 Treatment Guidelines Panel's Statement on Tixagevimab Plus Cilgavimab (Evusheld) as Pre-Exposure Prophylaxis of COVID-19

In the United States, the prevalence of subvariants likely to be resistant to tixagevimab plus cilgavimab (Evusheld) is more than 91%. Although tixagevimab plus cilgavimab is still authorized by the Food and Drug Administration (FDA) for COVID-19 pre-exposure prophylaxis (PrEP), it is unlikely to be effective at preventing COVID-19 in the vast majority of individuals. However, no alternative options for PrEP are available, and clinicians could still administer tixagevimab plus cilgavimab after considering an individual patient's risks and the regional prevalence of the resistant subvariants.

December 28, 2022

Updates Regarding the Use of Bebtelovimab

Due to the increasing prevalence of SARS-CoV-2 Omicron subvariants that are anticipated to be resistant to bebtelovimab (i.e., BQ.1, BQ.1.1, XBB), bebtelovimab is not currently authorized by the Food and Drug Administration (FDA) for the treatment of COVID-19 in any region of the United States. The Panel **recommends against** the use of **bebtelovimab** for the treatment of nonhospitalized patients with COVID-19 who are at high risk of progressing to severe COVID-19 **(AIII)**.

In this update, several sections of the Guidelines have been revised to reflect this recommendation. These sections include:

- Therapeutic Management of Nonhospitalized Adults With COVID-19
- Therapeutic Management of Nonhospitalized Children With COVID-19
- Antiviral Agents, Including Antibody Products
- Anti-SARS-CoV-2 Monoclonal Antibodies
- Table 4e

The COVID-19 Treatment Guidelines Panel's Statement on Tixagevimab Plus Cilgavimab (Evusheld) as Pre-Exposure Prophylaxis of COVID-19

Last Updated: January 10, 2023

The prevalence of SARS-CoV-2 Omicron subvariants likely to be resistant to tixagevimab plus cilgavimab (Evusheld) has been rapidly increasing in the United States. These subvariants are BA.2.75.2, BA.4.6, BA.5.2.6, BF.7, BF.11, BQ.1, BQ.1.1, and XBB.[1] In addition, the XBB.1.5 subvariant is not anticipated to be neutralized by tixagevimab plus cilgavimab.[2,3] As of January 6, 2023, the overall prevalence of these Omicron subvariants is estimated to be more than 91%.

Tixagevimab plus cilgavimab is authorized by the Food and Drug Administration (FDA) for pre-exposure prophylaxis (PrEP) of COVID-19 in people who are not expected to mount an adequate immune response to COVID-19 vaccination or people with contraindications for COVID-19 vaccination.

Due to the high prevalence of resistant Omicron subvariants in the United States, tixagevimab plus cilgavimab is unlikely to be effective at preventing COVID-19 in the vast majority of individuals, although it is still authorized by the FDA for COVID-19 PrEP. However, given the lack of alternative PrEP options, clinicians could still administer tixagevimab plus cilgavimab after considering an individual patient's risks and the regional prevalence of the resistant subvariants.

Regardless of their use of tixagevimab plus cilgavimab, it is crucial that these high-risk patients:

- Keep up to date with COVID-19 vaccination and boosters, unless contraindicated.
- Take precautions to avoid infection.
- Be tested for SARS-CoV-2 if they experience signs and symptoms consistent with COVID-19 and, if infected, promptly seek medical attention.

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Guidelines Development

Last Updated: December 1, 2022

The COVID-19 Treatment Guidelines were developed to provide clinicians with guidance on caring for patients with COVID-19. Because clinical information about the optimal management of COVID-19 is evolving quickly, these Guidelines are updated frequently to reflect newly published data and other authoritative information.

Panel Composition

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

The names and affiliations of the Panel members, ex officio members, consultants, and members of the Guidelines support team are provided in Appendix A, Table 1. Financial disclosures for the Panel members can be found in Appendix A, Table 2.

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 clinical information.

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

Method of Synthesizing Data and Formulating Recommendations

The working groups critically review and synthesize the available data to develop recommendations. During this process, the Panel evaluates the data, including the source of the data, the type of study (e.g., randomized controlled trial, prospective or retrospective cohort study, case series, in vitro study), the quality and suitability of the methods, the number of participants, and the effect sizes observed.

The recommendations in these Guidelines are based on scientific evidence and expert opinion. Each recommendation includes 2 ratings: an uppercase letter (**A**, **B**, or **C**) that indicates the strength of the recommendation and a Roman numeral with or without a lowercase letter (**I**, **IIa**, **IIb**, or **III**) that indicates the quality of the evidence that supports the recommendation (see Table 1).

The ratings for the quality of the evidence reflect both the likelihood of bias in the treatment effect estimate and the precision of the estimate. A rating of **I** corresponds to a low likelihood of bias and a high precision, a rating of **IIa** (for randomized trials) or **IIb** (for observational studies) corresponds to a moderate likelihood of bias and a moderate or high precision, and a rating of **III** corresponds to a high likelihood of bias (for any type of study).

Table 1. Recommendation Rating Scheme

Strength of Recommendation	Evidence for Recommendation
A: Strong recommendation for the statement	**I:** *High quality of evidence:* 1 or more randomized trials without major limitations,[a] well-powered subgroup analyses of such trials, or meta-analyses without major limitations
B: Moderate recommendation for the statement	**IIa:** *Moderate quality of evidence:* Randomized trials and subgroup analyses of randomized trials that do not meet the criteria for a **I** rating
C: Weak recommendation for the statement	**IIb:** *Moderate quality of evidence:* Observational studies without major limitations[b]
	III: Expert opinion

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

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

- **The Panel recommends using [blank] for the treatment of COVID-19 (rating).** Recommendations in this category are based on evidence that the potential benefits of using this

intervention outweigh the potential risks.

- **There is insufficient evidence for the Panel to recommend either for or against the use of [blank] for the treatment of COVID-19 (no rating).** This statement is used when there are currently not enough data to support a recommendation, or when the available data are conflicting.
- **The Panel recommends against the use of [blank] for the treatment of COVID-19, except in a clinical trial (rating)**. This recommendation is used in cases where the available data have shown no benefit of using this intervention for the treatment of COVID-19 and/or the intervention has demonstrated safety concerns. More results from clinical trials are needed to further define the role of these interventions in treating COVID-19.
- **The Panel recommends against the use of [blank] for the treatment of COVID-19 (rating).** This recommendation is used in cases where the available data show that there is no benefit of using this intervention to treat COVID-19 and/or the safety concerns for the intervention outweigh any potential benefits.

Evolving Knowledge on Treatments for COVID-19

Remdesivir and baricitinib are currently the only drugs approved by the Food and Drug Administration for the treatment of COVID-19. An array of drugs that are approved for other indications and multiple investigational agents are being studied for the treatment of COVID-19 in clinical trials around the globe. Information about these trials can be found at ClinicalTrials.gov. In addition, providers can access and prescribe investigational drugs or agents that are approved or licensed for other indications through various mechanisms, including Emergency Use Authorizations, Emergency Investigational New Drug applications, compassionate use or expanded access programs with drug manufacturers, and/or off-label use.

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

New data on the treatment of COVID-19 are emerging rapidly. Some of these data are being published in peer-reviewed journals, and some can be found in manuscripts that have not yet been peer reviewed or in press releases. The Panel continuously reviews the available data and assesses their scientific rigor and validity. These sources of data and the clinical experiences of the Panel members are used to determine whether new recommendations or changes to the current recommendations are warranted.

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

Overview of COVID-19

Last Updated: December 1, 2022

Epidemiology

Individuals of all ages are at risk for SARS-CoV-2 infection and severe disease. However, the probability of severe COVID-19 is higher in people aged ≥65 years, those living in a nursing home or long-term care facility, those who are not vaccinated against COVID-19 or who have poor responses to COVID-19 vaccines, and those with chronic medical conditions. Data on comorbid health conditions among patients with COVID-19 indicate that patients with cardiovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, diabetes with complications, neurocognitive disorders, and obesity are at increased risk of severe COVID-19. The risk appears to be higher in patients with multiple comorbid conditions. Other conditions that may lead to a high risk of severe COVID-19 include cancer, cystic fibrosis, immunocompromising conditions, liver disease (especially in patients with cirrhosis), pregnancy, and sickle cell disease. Transplant recipients and people who are taking immunosuppressive medications may also have a higher risk of severe COVID-19.[1] See Clinical Spectrum of SARS-CoV-2 Infection for a description of the clinical manifestations of SARS-CoV-2 infection and a discussion of the spectrum of disease.

Although COVID-19 vaccination does not eliminate the risk of SARS-CoV-2 infection, vaccination does significantly reduce the risk of COVID-19–related morbidity and mortality, particularly in individuals who are at high risk of progressing to severe disease.[2,3] In individuals who may not be able to mount adequate responses to COVID-19 vaccines due to immunocompromising conditions or the receipt of immunosuppressive medications, the use of the anti-SARS-CoV-2 monoclonal antibodies (mAbs) tixagevimab plus cilgavimab (Evusheld) as pre-exposure prophylaxis (PrEP) can reduce the risk of breakthrough infection and improve clinical outcomes.[4-6]

Racial and Ethnic Minorities and Other Marginalized Groups

Communities that have been historically marginalized or made socially vulnerable due to a lack of access to health care or an inability to socially isolate are at increased risk of SARS-CoV-2 acquisition, COVID-19–related hospitalization, and death. These communities include racial and ethnic minorities, essential non-health care workers, and some people with disabilities.

Key Considerations

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends that health care providers, health care systems, and payers ensure equitable access to high-quality care and treatment for all patients, regardless of race, ethnic identity, or other minoritized identity or social status **(AIII)**. "Minoritized" refers to social groups that have been deprived of power and status by the dominant culture in society and encompasses not just racial identities but other identities as well, including gender identity and sexual orientation.[7]
- Promoting equitable care for these groups must include considering the full range of medical, demographic, and social factors that may negatively impact health outcomes.
- Clinicians should also be aware that pulse oximeters may not accurately detect hypoxemia in people with darker skin pigmentation.[8,9] This may delay treatment and lead to worse clinical outcomes in patients with COVID-19.[10] See Clinical Spectrum of SARS-CoV-2 Infection for more information.

- Supporting equitable access to high-quality care and treatment for all groups is now an imperative for all Joint Commission-accredited health care organizations, as well as a priority for the Centers for Disease Control and Prevention (CDC) and other public health agencies.

COVID-19–Related Health Outcomes

Historical structural inequities significantly contribute to the health disparities experienced by racial and ethnic minority groups (e.g., Black/African American people, Hispanic people, American Indian/Alaska Native people).[11] Recent data have highlighted that some racial and ethnic minority groups experience higher rates of COVID-19, subsequent hospitalization, and death in relation to their share of the total U.S. population. Black/African American people, Hispanic people, and American Indian/Alaska Native people also experience rates of hospitalization that are more than 2 times higher and rates of COVID-19-related death that are approximately 2 times higher than those experienced by White people. The largest disparities were observed among American Indian/Alaska Native people, who experienced a rate of hospitalization almost 3 times higher and a rate of death 2.1 times higher than White people.[12]

The increased risk of severe COVID-19 among racial and ethnic minority groups may be partly attributed to higher rates of comorbid conditions in these populations (e.g., cardiovascular disease, diabetes, chronic kidney disease, hypertension, obesity, pulmonary diseases).[12]

Disparities in Access to Care

Members of racial and ethnic minority groups have an increased risk of exposure to COVID-19 and decreased access to care. Large-scale mobility data reveals that people living in lower-income communities were less able to physically isolate during COVID-19 emergency declarations,[13] as members of these communities were frequently unable to work from home.[14] A 2020 study evaluated access to health care resources in New York City and found that in areas of the city where the majority of the population was Black/African American and Hispanic, there were higher COVID-19 positivity rates and fewer licensed hospital beds and intensive care unit beds than in areas where the majority of the population was White.[15]

Disparities in Access to COVID-19 Treatments

Data from 41 U.S. health care systems reveal racial and ethnic disparities in the use of anti-SARS-CoV-2 mAbs for the treatment of COVID-19.[16] Black/African American patients, Asian patients, and patients of other races were, respectively, 22.4%, 48.3%, and 46.5% less likely to receive anti-SARS-CoV-2 mAbs for the treatment of COVID-19 than White patients.[16,17] Disparities have also been observed in the dispensing rates for ritonavir-boosted nirmatrelvir (Paxlovid) and molnupiravir. During the period when the use of outpatient COVID-19 medication was increasing substantially, treatment with ritonavir-boosted nirmatrelvir was 35.8% lower among Black/African American patients and 29.9% lower among Hispanic patients than among White patients.[18] Despite a greater number of dispensing sites in neighborhoods with a higher social vulnerability, oral antivirals were prescribed at a lower rate for patients with COVID-19 who were living in these areas than in those with a lesser degree of social vulnerability.[19] These disparities are not limited to outpatient settings. One retrospective cohort study of veterans hospitalized with COVID-19 reported that Black veterans had lower odds of receiving COVID-19–specific treatments, including systemic steroids, remdesivir, and immunomodulators, than White veterans.[20]

Other Marginalized Groups

Other marginalized groups also experience worse outcomes for COVID-19. Hospitalization rates for COVID-19 among Medicare beneficiaries who were eligible for disability were approximately

50% higher than those among people who were eligible for Medicare based on age alone, and this discrepancy disproportionately affected Black/African American people, Hispanic people, and American Indian/Alaska Native people.[21]

Migrants, refugees, and essential non-health care workers (e.g., food supply, food service, public transportation, and agricultural workers) also have disproportionately high rates of COVID-19 cases and deaths. These high rates can be attributed to overcrowding, an inability to physically isolate, and inadequate access to health care.[22-24]

Given the pervasiveness of disparities in access to care and provision of treatment, it is imperative for clinicians, working with others on the patient care team, to assess the social factors that contribute to access and quality gaps and to strive to provide equitable treatment to all patients. These issues have been identified as a strategic priority by the CDC and The Joint Commission.

SARS-CoV-2 Variants

Like other RNA viruses, SARS-CoV-2 is constantly evolving through random mutations. New mutations can potentially increase or decrease infectiousness and virulence. In addition, mutations can increase the virus' ability to evade adaptive immune responses from past SARS-CoV-2 infection or vaccination. This viral evolution may increase the risk of reinfection or decrease the efficacy of vaccines.[25] There is evidence that some SARS-CoV-2 variants have reduced susceptibility to plasma from people who were previously infected or immunized, as well as to certain anti-SARS-CoV-2 mAbs.[26-28]

Since December 2020, the World Health Organization (WHO) has assigned Greek letter designations to several identified variants. A SARS-CoV-2 variant designated as a variant of concern (VOC) displays certain characteristics, such as increased transmissibility or virulence. In addition, vaccines and therapeutics may have decreased effectiveness against VOCs, and the mutations found in these variants may interfere with the targets of diagnostic tests. The variant of interest (VOI) designation has been used for important variants that are not fully characterized; however, organizations do not use the same variant designations, and they may define their variant designations differently.[29,30] In September 2021, the CDC added a new designation for variants: variants being monitored (VBM). This refers to variants for which data indicate a potential or clear impact on approved or authorized medical countermeasures or variants associated with more severe disease or increased transmission rates. However, these variants are either no longer detected or are circulating at very low levels in the United States; therefore, they do not pose a significant and imminent risk to public health in the United States.

The Omicron variant was designated a VOC in November 2021 and rapidly became the dominant variant across the globe. The Omicron subvariants BA.1, BA.1.1, and BA.2 emerged in early to mid-2022. The subvariants BA.4 and BA.5 and, more recently, other subvariants such as BA.2.75, BA.4.6, BF.7, BQ.1, and BQ.1.1 are circulating in the United States. The newer Omicron subvariants are more transmissible than other variants and are not susceptible to some of the anti-SARS-CoV-2 mAbs that have been developed for treatment and prevention.[27,28,31,32]

Earlier variants include the Alpha (B.1.1.7) variant, which was first seen in the United Kingdom and shown to be highly infectious and possibly more virulent than previously reported variants;[33-35] the Beta (B.1.351) variant, which was originally identified in South Africa; the Gamma (P.1) variant, which was identified in Manaus, Brazil; and the Delta (B.1.617.2) variant, which was identified in India. Although the Alpha, Beta, Gamma, and Delta variants were previously designated as VOCs, they have largely disappeared worldwide. For a detailed discussion on the susceptibility of certain VOCs, VOIs, and VBMs to available anti-SARS-CoV-2 mAbs, please see Anti-SARS-CoV-2 Monoclonal Antibodies.

Data on the emergence, transmission, and clinical relevance of these new variants are rapidly evolving;

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

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Testing for SARS-CoV-2 Infection

Last Updated: August 8, 2022

Summary Recommendations
• The COVID-19 Treatment Guidelines Panel (the Panel) recommends using either a nucleic acid amplification test (NAAT) or an antigen test with a sample collected from the upper respiratory tract (e.g., nasopharyngeal, nasal mid-turbinate, anterior nasal) to diagnose acute SARS-CoV-2 infection **(AIII)**. • A NAAT should not be repeated in an asymptomatic person (with the exception of health care workers) within 90 days of a previous SARS-CoV-2 infection, even if the person has had a significant exposure to SARS-CoV-2 **(AIII)**. • SARS-CoV-2 reinfection has been reported in people after an initial diagnosis of the infection; therefore, clinicians should consider using a NAAT for those who have recovered from a previous infection and who present with symptoms that are compatible with SARS-CoV-2 infection if there is no alternative diagnosis **(BIII)**. • The Panel **recommends against** diagnosing acute SARS-CoV-2 infection solely on the basis of serologic (i.e., antibody) test results **(AIII)**. • There is insufficient evidence for the Panel to recommend either for or against the use of SARS-CoV-2 serologic testing to assess for immunity or to guide clinical decisions about using COVID-19 vaccines or anti-SARS-CoV-2 monoclonal antibodies.
Each recommendation in the Guidelines receives 2 ratings that reflect the strength of the recommendation and the quality of the evidence that supports it. See Guidelines Development for more information.

Diagnostic Testing for SARS-CoV-2 Infection

Everyone who has symptoms that are consistent with COVID-19 and people with known high-risk exposures to SARS-CoV-2 should be tested for SARS-CoV-2 infection. Such testing should employ either a nucleic acid amplification test (NAAT) or an antigen test to detect SARS-CoV-2. Testing may also be used for screening and determining the length of a patient's isolation period.[1]

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

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

Although nasopharyngeal specimens remain the recommended samples for SARS-CoV-2 diagnostic testing, nasal (anterior nares or mid-turbinate) or oropharyngeal swabs are acceptable alternatives.[3] Lower respiratory tract samples have a higher yield than upper respiratory tract samples, but they are often not obtained because of concerns about aerosolization of the virus during sample collection procedures. Some of the tests that have received EUAs can also be performed on saliva specimens, but the quality of saliva specimens can be highly variable. Studies are currently evaluating the use of other sample types, including stool samples.

Nucleic Acid Amplification Testing for SARS-CoV-2 Infection

Reverse transcription polymerase chain reaction (RT-PCR)-based diagnostic tests (which detect viral nucleic acids) are considered the gold standard for detecting current SARS-CoV-2 infection. More recently, NAATs have included isothermal amplification platforms (e.g., nicking endonuclease amplification reaction [NEAR], loop-mediated isothermal amplification [LAMP], transcription-mediated amplification [TMA]).[4] Some NAATs have also received EUAs for use in different settings, such as in laboratory facilities and point-of-care settings. Laboratory-based NAATs generally have higher sensitivity than point-of-care tests.[4]

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

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

SARS-CoV-2 poses several diagnostic challenges, including the potential for discordant viral shedding between the upper and lower respiratory tract. However, due to the high specificity of NAATs, a positive result on a NAAT of an upper respiratory tract sample from a patient with recent onset of SARS-CoV-2-compatible symptoms is sufficient to diagnose COVID-19. In patients with COVID-19, severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS), lower respiratory tract specimens have a higher viral load and thus a higher yield than upper respiratory tract specimens.[8-14]

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.[15,16] 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.[17,18] Furthermore, both virologic studies and contact tracing of high-risk contacts show a low risk for SARS-CoV-2 transmission after these intervals.[19,20] Based on these results, the Centers for Disease Control and Prevention (CDC) does not recommend repeating NAATs 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.[21] An exception to this is for health care workers who meet the specific criteria found in CDC guidance.[22] If there are concerns that an immunocompromised health care worker may still be infectious >20 days from the onset of SARS-CoV-2 infection, consulting local employee health services

about return-to-work testing policies is advised.

SARS-CoV-2 reinfection has been reported in people after an initial diagnosis of infection; therefore, clinicians should consider using a NAAT for those who have recovered from a previous infection and who present with symptoms that are compatible with SARS-CoV-2 infection if there is no alternative diagnosis **(BIII)**. However, a negative result on an initial NAAT followed by a positive result on a subsequent test does not necessarily mean a person has been reinfected, as this can occur due to intermittent detection of viral RNA.[15] When the results for an initial and a subsequent test are positive, comparative viral sequence data from both tests are needed to distinguish between the persistent presence of viral fragments and reinfection. In the absence of viral sequence data, the cycle threshold (Ct) value from a positive NAAT result may provide information about whether a newly detected infection is related to the persistence of viral fragments or to reinfection. The Ct value is the number of PCR cycles at which the nucleic acid target in the sample becomes detectable. In general, the Ct value is inversely related to the SARS-CoV-2 viral load. Because the clinical utility of Ct values is an area of active investigation, an expert should be consulted if these values are used to guide clinical decisions.

Antigen Testing for SARS-CoV-2 Infection

Antigen-based diagnostic tests (which detect viral antigens) are less sensitive than laboratory-based NAATs, but they have a similarly high specificity. Antigen tests perform best early in the course of symptomatic SARS-CoV-2 infection, when the viral load is thought to be highest. Early data suggest that antigen tests can detect the Omicron variant, but they may have lower sensitivity to this variant compared to earlier variants.[23] Advantages of antigen tests include their low cost and rapid turnaround time. The availability of immediate results makes them an attractive option for point-of-care testing in high-risk congregate settings (e.g., long-term care facilities, schools, dormitories, correctional facilities) and community settings, where preventing transmission is critical.

Increasingly, data are available to guide the use of antigen tests as screening tests to detect or exclude SARS-CoV-2 infection in asymptomatic persons, or to determine whether a person who was previously confirmed to have SARS-CoV-2 infection is still infectious. The CDC has developed an antigen testing algorithm for persons in congregate living settings and community settings who have symptoms of COVID-19, those who are asymptomatic and have a close contact with COVID-19, and those who are asymptomatic and have no known exposure to a person with COVID-19.[24] The CDC testing algorithm recommends performing additional confirmatory testing with a laboratory-based NAAT when a person who is strongly suspected of having SARS-CoV-2 infection (i.e., a person who is symptomatic) receives a negative result and when a person in a congregate living setting is asymptomatic but receives a positive result. People in congregate living settings who test positive for SARS-CoV-2 infection may need to be isolated as a group; therefore, correct identification of these individuals is especially important in this setting. People who are asymptomatic and have no known exposure to a person with COVID-19 should also undergo additional testing with a NAAT if they receive a positive result on an initial test.[24]

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, storing test cartridges/cards inappropriately);
- Test interference due to human antibodies (e.g., rheumatoid factor or other nonspecific antibodies); *and*
- Use in communities that have a low prevalence of SARS-CoV-2 infection.

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

Unlike NAATs and antigen tests for SARS-CoV-2 that detect the presence of the virus, serologic or antibody tests can detect recent or prior SARS-CoV-2 infection. Because it may take 21 days or longer after symptom onset for seroconversion to occur (i.e., the development of detectable immunoglobulin [Ig] M and/or IgG antibodies to SARS-CoV-2),[25-30] the Panel **does not recommend** using serologic testing as the sole basis for diagnosing acute SARS-CoV-2 infection **(AIII)**. Because NAATs and antigen tests for SARS-CoV-2 occasionally yield false negative results, serologic tests have been used in some settings as an additional diagnostic test for patients who are strongly suspected to have SARS-CoV-2 infection. Using a serologic test in combination with a NAAT to detect IgG or total antibodies 3 to 4 weeks after symptom onset maximizes the sensitivity and specificity to detect past infection.

No serologic tests for SARS-CoV-2 are approved by the FDA; some, but not all, commercially available serologic tests for SARS-CoV-2 have received EUAs from the FDA.[31] Several professional societies and federal agencies, including the Infectious Diseases Society of America, the CDC, and the FDA, provide guidance on the use of serologic testing for SARS-CoV-2.

Several factors should be considered when using serologic tests, including:

- Important performance characteristics of many of the commercially available serologic tests have not been fully characterized, including the sensitivity and specificity of these tests (i.e., the rates of true positive and true negative results). Only serologic assays that have FDA EUAs should be used in public health or clinical settings. Formal comparisons of serologic tests are in progress.
- Two types of serologic tests have received EUAs from the FDA. The first type are antibody tests that detect the presence of binding antibodies, which bind to a pathogen (e.g., a virus). The second type detects neutralizing antibodies from recent or prior SARS-CoV-2 infection. It is unknown whether either type of test is more clinically useful than the other.
- Serologic assays may detect IgM, IgG, or IgA antibodies, or certain combinations of these antibodies. Some assays may also detect total antibodies. Serologic assays that detect IgG and total antibodies have a 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 FDA has issued EUAs for more than 80 SARS-CoV-2 serologic tests since the start of the pandemic. However, these tests are not currently authorized for routine use in making individual medical decisions.[31] SARS-CoV-2 serologic tests are authorized for detecting antibodies, but their ability to predict protective immunity has not been validated. The majority of these tests are not standardized. Furthermore, as SARS-CoV-2 is not a well-conserved virus, mutations in the receptor binding domain of the virus could lead to decreased binding affinity between antibodies and SARS-CoV-2-specific antigens.

There is currently insufficient evidence for the Panel to recommend either for or against the use of SARS-CoV-2 serologic testing to assess for immunity or to guide clinical decisions about using COVID-19 vaccines or anti-SARS-CoV-2 monoclonal antibodies.

If a serologic test is performed, the result should be interpreted with caution. First, it remains unclear how long SARS-CoV-2 antibodies persist following either infection or vaccination. A negative serologic test result also does not preclude prior SARS-CoV-2 infection or vaccination against COVID-19. Second, some people who are infected with SARS-CoV-2 or who are vaccinated against COVID-19 may

not develop measurable antibodies (e.g., those who are immunocompromised). It is presumed that those who do not have measurable antibodies after vaccination are at higher risk of SARS-CoV-2 infection than those who have measurable antibodies. Third, because nucleocapsid proteins are not a constituent of the vaccines that are currently approved by the FDA, available through EUAs, or in late-stage clinical trials, serologic tests that detect antibodies by recognizing nucleocapsid proteins should be used to distinguish between antibody responses to natural infection and vaccine-induced antibody responses to the SARS-CoV-2 spike protein antigen.

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

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

- Determine who may be eligible to donate convalescent plasma;
- Define multisystem inflammatory syndrome in children (MIS-C) and multisystem inflammatory syndrome in adults (MIS-A); *or*
- Estimate the proportion of the population that has been exposed to SARS-CoV-2.

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Prevention of SARS-CoV-2 Infection

Last Updated: December 1, 2022

Summary Recommendations

Vaccines

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends COVID-19 vaccination as soon as possible for everyone who is eligible according to the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices **(AI)**.

Pre-Exposure Prophylaxis

- The circulation of Omicron subvariants that are resistant to tixagevimab plus cilgavimab (Evusheld) has been increasing in the United States.
- Tixagevimab plus cilgavimab is the only agent authorized by the Food and Drug Administration for use as SARS-CoV-2 pre-exposure prophylaxis (PrEP) in people who are not expected to mount an adequate immune response to COVID-19 vaccination or those with contraindications for COVID-19 vaccines.
- In the absence of an alternative option for PrEP, the Panel recommends the use of **tixagevimab 300 mg plus cilgavimab 300 mg** administered as 2 consecutive 3-mL intramuscular (IM) injections **(BIIb**) as SARS-CoV-2 PrEP for adults and adolescents (aged ≥12 years and weighing ≥40 kg) who do not have SARS-CoV-2 infection, who have not been recently exposed to an individual with SARS-CoV-2 infection, **AND** who:
  - Are moderately to severely immunocompromised and may have an inadequate immune response to COVID-19 vaccination; *or*
  - Are not able to be fully vaccinated with any available COVID-19 vaccines due to a history of severe adverse reactions to a COVID-19 vaccine or any of its components.
- For individuals who only received tixagevimab 150 mg plus cilgavimab 150 mg, a tixagevimab 300 mg plus cilgavimab 300 mg dose should be administered as soon as possible.
- The Panel recommends repeat dosing of **tixagevimab 300 mg plus cilgavimab 300 mg** administered as IM injections every 6 months **(BIIb)**.
- Certain Omicron subvariants may have markedly reduced in vitro susceptibility to tixagevimab plus cilgavimab, which could result in reduced efficacy.
- The decision to administer tixagevimab plus cilgavimab should be based on the regional prevalence of the resistant subvariants, the individual patient's risks, the available resources, and logistics.
- Individuals who receive tixagevimab plus cilgavimab as PrEP should continue to take precautions to avoid infection. If they experience signs and symptoms consistent with COVID-19, they should be tested for SARS-CoV-2 and, if infected, promptly seek medical attention.
- **Tixagevimab plus cilgavimab is not a substitute for COVID-19 vaccination and should not be used in unvaccinated individuals for whom COVID-19 vaccination is recommended.**

Each recommendation in the Guidelines receives 2 ratings that reflect the strength of the recommendation and the quality of the evidence that supports it. See Guidelines Development for more information.

General Prevention Measures

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

Less commonly, airborne transmission of droplets and particles of SARS-CoV-2 to people farther than

6 feet away can occur. In rare cases, people passing through a room that was previously occupied by an infectious person may become infected. SARS-CoV-2 infection via airborne transmission of small particles tends to occur after prolonged exposure (i.e., >15 minutes) to an infectious person who is in an enclosed space with poor ventilation.[1]

The risk of SARS-CoV-2 transmission can be reduced by covering coughs and sneezes and maintaining a distance of at least 6 feet from others. When consistent distancing is not possible, face coverings may reduce the spread of infectious droplets from individuals with SARS-CoV-2 infection to others. Frequent handwashing also effectively reduces the risk of infection.[2] Health care providers should follow the Centers for Disease Control and Prevention (CDC) recommendations for infection control and the appropriate use of personal protective equipment.[3]

Vaccines

Vaccination is the most effective way to prevent SARS-CoV-2 infection. The COVID-19 Treatment Guidelines Panel (the Panel) recommends COVID-19 vaccination as soon as possible for everyone who is eligible according to the CDC's Advisory Committee on Immunization Practices **(AI)**. Four vaccines are authorized or approved for use in the United States to prevent COVID-19. For primary and booster vaccinations, the mRNA vaccines BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) and the recombinant spike protein with matrix-M1 adjuvant vaccine NVX-CoV2373 (Novavax) are preferable to the adenovirus vector vaccine Ad26.COV2.S (Johnson & Johnson/Janssen) due to its risk of serious adverse events.[4]

A primary series of COVID-19 vaccinations is recommended for everyone aged ≥6 months in the United States. The Food and Drug Administration (FDA) Emergency Use Authorization (EUA) fact sheet and the product label for each vaccine provide detailed information on the vaccination schedule and doses approved or authorized for that vaccine. Bivalent mRNA vaccines that protect against the original SARS-CoV-2 virus strain and Omicron subvariants BA.4 and BA.5 are now recommended for individuals at least 2 months after receiving the primary vaccine series or a booster dose. The type and dose of vaccine and the timing of these additional doses depend on the recipient's age and underlying medical conditions. The CDC regularly updates the clinical considerations for use of the COVID-19 vaccines currently approved by the FDA or authorized for use in the United States.[5]

Adverse Events

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

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

hematologist should be considered for patients with TTS.

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

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

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

Vaccination in Pregnant or Lactating People

Pregnant and lactating individuals were not included in the initial COVID-19 vaccine trials. However, the CDC, the American College of Obstetricians and Gynecologists (ACOG), and the Society for Maternal-Fetal Medicine recommend vaccination for pregnant and lactating people based on the accumulated safety and efficacy data on the use of these vaccines in pregnant people, as well as the increased risk of severe disease in pregnant individuals with COVID-19.[12-17] These organizations also recommend vaccination for people who are trying to become pregnant or who may become pregnant in the future. The ACOG publication includes a guide for clinicians on counseling pregnant patients about COVID-19 vaccination.[18]

Pre-Exposure Prophylaxis

Anti-SARS-CoV-2 Monoclonal Antibodies

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

On the basis of results from PROVENT, a large randomized controlled trial conducted when the major circulating SARS-CoV-2 variants were Alpha, Beta, Delta, and Epsilon,[19] the FDA issued an EUA for the anti-SARS-CoV-2 monoclonal antibodies (mAbs) tixagevimab plus cilgavimab (Evusheld).[20] The EUA allows these anti-SARS-CoV-2 mAbs to be used as pre-exposure prophylaxis (PrEP) for certain individuals who are immunocompromised and therefore may have inadequate responses to COVID-19 vaccines or are unable to be fully vaccinated due to a history of severe adverse reactions to a COVID-19 vaccine. A modification in the fragment crystallizable (Fc) region gives these anti-SARS-CoV-2 mAbs prolonged half-lives, resulting in potential protection from SARS-CoV-2 infection for up to 6 months, depending on the variant.

The PROVENT trial used tixagevimab 150 mg plus cilgavimab 150 mg, which was the dose initially authorized by the FDA. However, in vitro data indicated that the Omicron subvariants BA.4 and BA.5 had decreased susceptibility to tixagevimab plus cilgavimab. Because of these findings, in February 2022, the FDA revised the EUA to authorize the use of an increased dose of tixagevimab 300 mg plus cilgavimab 300 mg.[20-23] For individuals who only received tixagevimab 150 mg plus cilgavimab 150 mg, a tixagevimab 300 mg plus cilgavimab 300 mg dose should be administered as soon as possible. On June 30, 2022, the FDA further revised the EUA to authorize repeated doses of tixagevimab 300 mg plus cilgavimab 300 mg to be administered every 6 months.

The prevalence of certain Omicron subvariants (i.e., BA.4.6, BA.2.75.2, BA.5.2.6, BF.7, BQ.1,

BQ.1.1) that are resistant to tixagevimab plus cilgavimab is rapidly increasing. However, tixagevimab plus cilgavimab is the only agent authorized by the FDA for use as SARS-CoV-2 PrEP in people who are not expected to mount an adequate immune response to COVID-19 vaccination or those with contraindications for COVID-19 vaccines. Therefore, the Panel recommends the use of **tixagevimab plus cilgavimab** as PrEP for eligible individuals **(BIIb)**.

When prescribing tixagevimab plus cilgavimab for SARS-CoV-2 PrEP, clinicians should be aware of the following:

- Tixagevimab plus cilgavimab is authorized for use as PrEP in a population that was not well represented in the PROVENT trial (i.e., a very small proportion of the participants were immunocompromised).
- There are no clinical trial efficacy data on the tixagevimab 300 mg plus cilgavimab 300 mg dose administered for the prevention of symptomatic COVID-19, and there are no data for any repeated dose at any defined interval. This dose and the strategy of repeating the dose every 6 months are based on pharmacokinetic/pharmacodynamic (PK/PD) modeling data.[24] Substantial uncertainty in the PK/PD model remains.
- Safety data on the use of tixagevimab 300 mg plus cilgavimab 300 mg primarily come from TACKLE, a Phase 3 clinical trial that evaluated single doses of tixagevimab plus cilgavimab for the treatment of patients with mild to moderate COVID-19.[24,25]

Recommendations

Factoring in the limitations outlined above:

- The Panel recommends the use of **tixagevimab 300 mg plus cilgavimab 300 mg** administered as 2 consecutive 3-mL intramuscular (IM) injections **(BIIb)** as SARS-CoV-2 PrEP for adults and adolescents (aged ≥12 years and weighing ≥40 kg) who do not have SARS-CoV-2 infection, who have not been recently exposed to an individual with SARS-CoV-2 infection, **AND** who:
  - Are moderately to severely immunocompromised and may have an inadequate immune response to COVID-19 vaccination; *or*
  - Are not able to be fully vaccinated with any available COVID-19 vaccines due to a history of severe adverse reactions to a COVID-19 vaccine or any of its components.
- For individuals who only received tixagevimab 150 mg plus cilgavimab 150 mg, a tixagevimab 300 mg plus cilgavimab 300 mg dose should be administered as soon as possible.
- Given the increasing prevalence of resistant SARS-CoV-2 subvariants, the decision to administer tixagevimab plus cilgavimab should be based on the regional prevalence of the resistant subvariants, the individual patient's risks, the available resources, and logistics. The Panel's recommendations for the use of tixagevimab plus cilgavimab may change if the prevalence of resistant subvariants increases.
- Individuals who receive tixagevimab plus cilgavimab as PrEP should continue to take precautions to avoid infection. If they experience signs and symptoms consistent with COVID-19, they should be tested for SARS-CoV-2 and, if infected, promptly seek medical attention.
- The Panel recommends repeat dosing of **tixagevimab 300 mg plus cilgavimab 300 mg** administered as IM injections every 6 months **(BIIb)**. Repeat doses should be timed from the most recent dose of tixagevimab plus cilgavimab.
- **Tixagevimab plus cilgavimab is not a substitute for COVID-19 vaccination and should not be used in unvaccinated individuals for whom COVID-19 vaccination is recommended.**

Additional Considerations

- Evusheld contains the ingredient polysorbate 80, which is structurally related to polyethylene glycol.[20] COVID-19 vaccines approved or authorized by the FDA contain either polysorbate 80 or polyethylene glycol. There is a theoretical risk of cross-hypersensitivity between Evusheld and COVID-19 vaccines. Before administering Evusheld to individuals with a history of severe hypersensitivity reactions to a COVID-19 vaccine, consultation with an allergist/immunologist should be considered.
- Individuals who qualify as having moderate to severe immunocompromising conditions under the FDA EUA for tixagevimab plus cilgavimab include, but are not limited to, those who:
  - Are receiving active treatment for solid tumors and hematologic malignancies.
  - Have a hematologic malignancy (e.g., chronic lymphocytic leukemia, non-Hodgkin lymphoma, multiple myeloma, acute leukemia) that has been associated with poor response to COVID-19 vaccines, regardless of the patient's current treatment.
  - Received a solid organ or islet transplant and are receiving immunosuppressive therapy.
  - Received chimeric antigen receptor T cell therapy or a hematopoietic cell transplant (and are within 2 years of transplantation or are receiving immunosuppressive therapy).
  - Have a moderate or severe primary immunodeficiency (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome).
  - Have advanced or untreated HIV infection (defined as people with HIV and CD4 T lymphocyte cell counts <200 cells/mm^3, a history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV).
  - Are receiving active treatment with high-dose corticosteroids (i.e., ≥20 mg prednisone or equivalent per day when administered for ≥2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, or immunosuppressive or immunomodulatory biologic agents (e.g., B cell-depleting agents).
- The strength of the Panel's current recommendation for tixagevimab 300 mg plus cilgavimab 300 mg is based partly on PK/PD modeling for the Omicron BA.1 and BA.1.1 subvariants and partly on the BA.2 subvariant's near-full susceptibility to tixagevimab plus cilgavimab shown in vitro.[26] The Panel's recommendation may change if subvariants with reduced susceptibility to tixagevimab plus cilgavimab become more prevalent.
- If supplies of tixagevimab plus cilgavimab are limited, priority for use as PrEP should be given to those who are at the highest risk for severe COVID-19.
- If a person has received a COVID-19 vaccine, tixagevimab plus cilgavimab should be administered at least 2 weeks after vaccination.

Clinical Trial Data for Tixagevimab Plus Cilgavimab

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

The analyzed population included participants who received a negative reverse transcription polymerase

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

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

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

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

Other Drugs for Pre-Exposure Prophylaxis

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

Clinical trials are investigating several agents, including emtricitabine plus tenofovir alafenamide or tenofovir disoproxil fumarate; hydroxychloroquine; ivermectin; and supplements such as zinc, vitamin C, and vitamin D.

Hydroxychloroquine, given at different doses and durations, has been studied in randomized controlled trials to assess whether it could prevent SARS-CoV-2 infection in those at risk of being exposed to infected individuals, such as health care workers. One study reported no evidence of a benefit of hydroxychloroquine, and it was ultimately halted due to futility before it reached its target enrollment.[27] 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.[28] Neither

study demonstrated any evidence of a reduction in the rate of acquiring infection. Both studies reported an increased frequency of mild adverse events in the treatment group.

Post-Exposure Prophylaxis

Anti-SARS-CoV-2 Monoclonal Antibodies

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

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

Chloroquine and Hydroxychloroquine

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

Both chloroquine and hydroxychloroquine have in vitro activity against SARS-CoV and SARS-CoV-2.[29,30] A small cohort study without a control group suggested that hydroxychloroquine might reduce the risk of SARS-CoV-2 transmission to close contacts.[31] There have been several large trials to determine whether hydroxychloroquine can reduce the risk of infection after exposure to individuals infected with SARS-CoV-2. These studies used different dose schedules and targeted different at-risk populations. In addition, some studies were unable to confirm infection using molecular or antigen tests. None of these studies demonstrated any evidence of efficacy for hydroxychloroquine, and all showed a higher risk of generally mild adverse events in those who received the drug.[32-34]

Other Drugs for Post-Exposure Prophylaxis

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

A number of other agents (e.g., ivermectin, hyperimmune gamma globulin, COVID-19 convalescent plasma, interferons, tenofovir with or without emtricitabine, vitamin D) have been studied for SARS-CoV-2 PEP. The Panel recommends against their use as SARS-CoV-2 PEP because the studies of these agents have not demonstrated sufficient benefit.

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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 measured by pulse oximetry (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.

SpO_2 is a key parameter for defining the illness categories listed above. However, pulse oximetry has important limitations (discussed in more detail below). Clinicians who use SpO_2 when assessing a patient must be aware of those limitations and conduct the assessment in the context of that patient's clinical status.

Patients who are aged ≥65 years are at a higher risk of progressing to severe COVID-19. Other underlying conditions associated with a higher risk of severe COVID-19 include asthma, cancer, cardiovascular disease, chronic kidney disease, chronic liver disease, chronic lung disease, diabetes, advanced or untreated HIV infection, obesity, pregnancy, cigarette smoking, and being a recipient of immunosuppressive therapy or a transplant.[1] Health care providers should closely monitor patients with these conditions until they achieve clinical recovery.

The initial evaluation for patients may include chest imaging (e.g., X-ray, ultrasound or computed tomography scan) and an electrocardiogram. Laboratory testing should include 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 also apply to pregnant patients. However, the threshold for certain interventions is different for pregnant patients and nonpregnant patients. For example, oxygen supplementation for pregnant patients is generally used when SpO_2 falls below 95% on room air at sea level to accommodate the 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 subsections in 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 subset of children and young adults, SARS-CoV-2 infection may be followed by the severe inflammatory condition multisystem inflammatory syndrome in children (MIS-C).[8,9] This syndrome is discussed in detail in Special Considerations in Children.

Clinical Considerations for the Use of Pulse Oximetry

During the COVID-19 pandemic, the use of pulse oximetry to assess and monitor patients' oxygenation status increased in hospital, outpatient health care facility, and home settings. Although pulse oximetry is useful for estimating blood oxygen levels, pulse oximeters may not accurately detect hypoxemia under certain circumstances. To avoid delays in recognizing hypoxemia, clinicians who use pulse oximetry to assist with clinical decisions should keep these limitations in mind.

Pulse oximetry results can be affected by skin pigmentation, thickness, or temperature. Poor blood circulation or the use of tobacco or fingernail polish also may affect results. The Food and Drug Administration (FDA) advises clinicians to refer to the label or manufacturer website of a pulse oximeter or sensor to ascertain its accuracy.[10] The FDA also advises using pulse oximetry only as an estimate of blood oxygen saturation, because an SpO_2 reading represents a range of arterial oxygen saturation (SaO_2). For example, an SpO_2 reading of 90% may represent a range of SaO_2 from 86% to 94%.

Several published reports have compared measurements of SpO_2 and SaO_2 in patients with and without COVID-19. The studies demonstrated that occult hypoxemia (defined as SaO_2 <88% despite SpO_2 >92%) was more common in patients with darker skin pigmentation, which may result in adverse consequences.[11-13] The likelihood of error was greater in the lower ranges of SpO_2. In 2 studies, greater incidences of occult hypoxemia were observed in patients who were Black, Hispanic, or Asian than in patients who were White.[11,12] In 1 of these studies, occult hypoxemia was associated with more organ dysfunction and hospital mortality.[13]

A 5-hospital registry study of patients evaluated in the emergency department or hospitalized for COVID-19 found that 24% were not identified as eligible for treatment due to overestimation of SaO_2. The majority of patients (55%) who were not identified as eligible were Black. The study also examined the amount of time delay patients experienced before their treatment eligibility was identified. The median delay for patients who were Black was 1 hour longer than for those who were White.[14]

In pulse oximetry, skin tone is an important variable, but accurately measuring oxygen saturation is a complex process. One observational study in adults was unable to identify a consistently predictable difference between SaO_2 and SpO_2 over time for individual patients.[11] Factors other than skin pigmentation (e.g., peripheral perfusion, pulse oximeter sensor placement) are likely involved.

Despite the limitations of pulse oximetry, an FDA-cleared pulse oximeter for home use can contribute to an assessment of a patient's overall clinical status. Practitioners should advise patients to follow the manufacturer's instructions for use, place the oximeter on the index or ring finger, and ensure the hand

is warm, relaxed, and held below the level of the heart. Fingernail polish should be removed before testing. Patients should be at rest, indoors, and breathing quietly without talking for several minutes before testing. Rather than accepting the first reading, patients or caretakers should observe the readings on the pulse oximeter for ≥30 seconds until a steady number is displayed.[10,15] Patients should inform their health care provider if the reading is repeatedly below a previously specified value (generally 95% on room air at sea level). Pulse oximetry has been widely adopted as a remote patient monitoring tool, but when the use of pulse oximeters is compared with close monitoring of clinical progress via video consultation, telephone calls, text messaging, or home visits, there is insufficient evidence that it improves clinical outcomes.[16,17]

Not all commercially available pulse oximeters have been cleared by the FDA. SpO_2 readings obtained through non-FDA-cleared devices, such as over-the-counter sports oximeters or mobile phone applications, lack sufficient accuracy for clinical use. Abnormal readings on these devices should be confirmed with an FDA-cleared device or an arterial blood gas analysis.[18,19]

Regardless of the setting, SpO_2 should always be interpreted within the context of a patient's entire clinical presentation. A patient's signs and symptoms (e.g., dyspnea, tachypnea, chest pain, changes in cognition or attentional state, cyanosis) should be given greater weight than a pulse oximetry result.

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 consistent with COVID-19 pneumonia.[20,21]

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 patients who are mildly ill 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 anti-SARS-CoV-2 therapies.

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. See Therapeutic Management of Nonhospitalized Adults With COVID-19 for recommendations regarding anti-SARS-CoV-2 therapies. If bacterial pneumonia is suspected, administer empiric antibiotic treatment, re-evaluate the patient daily, and de-escalate or stop antibiotics if further testing indicates the patient does not have a bacterial infection.

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 anti-SARS-CoV-2 therapies. If bacterial pneumonia or sepsis is suspected, administer empiric antibiotics, re-evaluate the patient daily, and de-escalate or stop antibiotics if further testing indicates the patient does not have a bacterial infection.

Critical Illness

SARS-CoV-2 infection can cause acute respiratory distress syndrome, virus-induced distributive (septic) shock, cardiac shock, an exaggerated inflammatory response, thrombotic disease, and exacerbation of underlying comorbidities.

Successful clinical management of a patient with COVID-19, as with any patient in the intensive care unit (ICU), includes treating both the medical condition that initially resulted in ICU admission as well as other comorbidities and nosocomial complications. For more information, see Critical Care for Adults.

Infectious Complications in Patients With COVID-19

Some patients with COVID-19 may have additional infections 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:* Although most individuals present with only SARS-CoV-2 infection, concomitant viral infections, including influenza and other respiratory viruses, have been reported.[22] 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.[22,23] 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,[24-26] although the data are currently limited. Reactivation of herpes simplex virus and varicella zoster virus infections have also been reported.[27] Cases of severe and disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with tocilizumab and corticosteroids.[28,29] Many clinicians would initiate empiric treatment (e.g., with the antiparasitic drug ivermectin), with or without serologic testing, in patients who are from areas where *Strongyloides* is endemic (i.e., tropical, subtropical, or warm temperate areas).[30]
- *Nosocomial infections:* 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.[31-34] Although these infections are relatively rare, they can be fatal, and they may be seen more commonly in patients who are immunocompromised or receiving mechanical ventilation. The majority of mucormycosis cases have been reported in India and are associated with diabetes mellitus or the use of corticosteroids.[35,36] 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 and Breakthrough Infection

As seen with other viral infections, reinfection after recovery from prior infection has been reported for SARS-CoV-2.[37] Reinfection may occur as initial immune responses to the primary infection wane over time. The true prevalence of reinfection is not known and likely varies depending on the circulating variants. A national database study in Qatar estimated that previous infection prevented reinfection with the Alpha, Beta, and Delta variants of concern (VOCs), with 90%, 86%, and 92% effectiveness, respectively. Protection against reinfection with the Omicron VOC was about 56% effective.[38] Furthermore, an investigation of Omicron infection after Delta infection in 4 U.S. states identified 10 cases of reinfection that occurred <90 days after a symptomatic infection (1 reinfection required hospitalization).[39] The majority of reinfection cases (70%) occurred in people who were unvaccinated. Fewer patients were symptomatic during reinfection than during the initial infection. Among patients who were symptomatic, the median duration of symptoms was shorter with reinfection than with the initial infection.

Breakthrough SARS-CoV-2 infections (i.e., infection in people who completed the primary vaccine series) have been reported.[40] Breakthrough SARS-CoV-2 infection appears to be less likely to lead to severe illness than infection in people who are unvaccinated. An analysis of electronic health record data from a large U.S. sample of 664,722 patients seen from December 2020 to September 2021 found that full vaccination was associated with a 28% reduction in the risk of a breakthrough infection.[40] That study also found that the time to breakthrough infection was shorter for patients with immunocompromising conditions (i.e., people with HIV or solid organ or bone marrow transplant recipients) than for those with no immunocompromising conditions. For information on diagnostic testing in the setting of suspected reinfection, see Testing for SARS-CoV-2 Infection. In addition, guidelines for the diagnosis and evaluation of suspected SARS-CoV-2 reinfection or breakthrough infection are provided by the Centers for Disease Control and Prevention (CDC).

Although data are limited, no evidence suggests that the treatment of suspected or documented SARS-CoV-2 reinfection or breakthrough infection 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 and Other Conditions After Acute COVID-19

Some patients may experience persistent symptoms or other conditions after acute COVID-19. Adult and pediatric data on the incidence, natural history, and etiology of these symptoms and organ dysfunction are emerging. However, reports on these data have several limitations, including differing case definitions. In addition, many reports only included patients who attended post-COVID clinics, and the studies often lack comparator groups. No specific treatments for persistent effects of COVID-19 have been shown to be effective, although general management strategies have been proposed, including interim guidance from the CDC, the American Academy of Physical Medicine and Rehabilitation, and the United Kingdom's COVID-19 rapid guideline.

The nomenclature for this phenomenon is evolving, and no clinical terminology has been established. It has been referred to as post-COVID condition, post-COVID syndrome, post-acute sequelae of SARS-CoV-2, or, colloquially, "long COVID." Affected patients have been referred to as "long haulers." MIS-C and multisystem inflammatory syndrome in adults (MIS-A) are serious postinfectious complications of acute COVID-19. For more information on these syndromes, see Therapeutic Management of Hospitalized Pediatric Patients With Multisystem Inflammatory Syndrome in Children (MIS-C) (With Discussion on Multisystem Inflammatory Syndrome in Adults [MIS-A]).

The CDC has defined post-COVID conditions as new, returning, or ongoing symptoms that people experience ≥4 weeks after being infected with SARS-CoV-2.[41] In October 2021, the World Health Organization published a clinical case definition that described the post-COVID clinical condition as usually occurring 3 months after the onset of COVID-19 with symptoms that last for ≥2 months and cannot be explained by an alternative diagnosis.[42]

Persistent Symptoms

The prevalence of persistent post-COVID clinical signs and symptoms remains unclear. In a systematic review of 25 observational cohort studies, prevalence varied widely (from 5% to 80%) and likely reflected differences in study populations, case definitions, and data resources.[43] Another large, systematic review found a similar prevalence of post-COVID symptoms 6 months after initial infection between studies from high-income or low- and middle-income countries and between studies in which >60% or <60% of the patients were hospitalized.[44]

A prospective study conducted at the University of Washington investigated mostly outpatients with laboratory-confirmed SARS-CoV-2 infection (150 participants had mild illness, 11 had no symptoms, and 11 had moderate or severe disease that required hospitalization).[45] Participants completed a follow-up questionnaire 3 months to 9 months after illness onset; 33% of outpatients and 31% of hospitalized patients reported ≥1 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.

In these and other studies, the most commonly reported nonneurologic, persistent symptoms included fatigue or muscle weakness, joint pain, chest pain, palpitations, shortness of breath, and cough.[44-51] From January 2020 to April 2021, the CDC conducted an internet-based survey of 3,135 noninstitutionalized adults who self-reported receiving either a positive or negative SARS-CoV-2 test result.[52] The study found that fatigue, shortness of breath, and cough were commonly reported symptoms lasting >4 weeks after onset. The prevalence of these symptoms among participants with a positive test result versus the prevalence among participants with a negative test result was 22.5% versus 12% for fatigue, 15.5% versus 5.2% for shortness of breath, and 14.5% versus 4.9% for cough.

Some of the reported symptoms overlap with post-intensive care syndrome symptoms that have been described for patients without COVID-19. Prolonged symptoms and disabilities after COVID-19 have also been reported in patients with milder illness, including outpatients.[53,54]

Patients who had breakthrough infection after COVID-19 vaccination are less likely to report symptoms that persist ≥28 days than patients with SARS-CoV-2 infection who are unvaccinated.[55,56] The COVID Symptom Study, conducted from December 2020 to July 2021, included participants who used a mobile application to report symptoms after breakthrough infections or reinfection.[46] The investigators found that the odds of reporting symptoms for ≥28 days was reduced by about half among participants who received 2 vaccine doses, when compared with participants who received 1 or 0 vaccine doses.

A study of electronic health record data from 59 health care organizations, primarily in the United States, compared the records of people who did not receive any vaccine doses with records of people

who received 2 vaccine doses.[57] In the 6 months after infection, those who received 2 vaccine doses had a lower risk for some, but not all, long-COVID outcomes, such as fatigue, muscle weakness, loss of the sense of smell, or hair loss.

Cardiopulmonary Injury

A U.S. Department of Veterans Affairs (VA) study of a national health care database compared 153,760 veterans who survived the first 30 days of COVID-19 to contemporary and historical control cohorts that had no evidence of SARS-CoV-2 infection.[58] When compared with the control cohorts, patients with history of COVID-19 had a greater incidence of post-acute cardiovascular outcomes (e.g., cerebrovascular disorder, dysrhythmia, inflammatory heart disease, ischemic heart disease, heart failure, thromboembolic disease) at 12 months.

A prospective study of pulmonary function examined longitudinal data from the adult Copenhagen General Population Study and found that pulmonary function declined faster for the 107 patients with mostly mild COVID-19 than for a matched sample from the general population.[59]

Neuropsychiatric Impairment

Neuropsychiatric impairments have been reported among patients who have recovered from acute COVID-19. Reported persistent neurologic symptoms include headaches, vision changes, hearing loss, impaired mobility, numbness in extremities, restless legs syndrome, tremors, memory loss, cognitive impairment, sleep difficulties, concentration problems, mood changes, and loss of smell or taste.[60-63]

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.[64] However, the study authors did not report when the tests were administered in relation to the diagnosis of COVID-19.

A retrospective cohort study examined the electronic health records of 273,618 patients from 59 health care organizations, primarily in the United States.[65] The study reported that cognitive dysfunction (defined using International Classification of Diseases, Tenth Revision codes) 3 to 6 months after diagnosis was worse for people with COVID-19 than for people with influenza. Other studies have reported high rates of anxiety and depression among patients who evaluated their psychiatric distress using self-report scales.[51,66] Reports also show that patients aged ≤60 years experienced more psychiatric symptoms than patients aged >60 years.[50,51]

Metabolic Perturbations

There have been reports of new-onset diabetes after COVID-19.[67] A study of a VA national health care database analyzed the records of 181,280 people who survived the first 30 days of COVID-19 and compared them to a contemporary control cohort that had no evidence of SARS-CoV-2 infection. People with a history of COVID-19 had a 40% greater risk of diabetes 12 months after infection than people in the control cohort.[68] A CDC study of people aged <18 years reported that those with a history of COVID-19 had an increased risk of diabetes >30 days after SARS-CoV-2 infection when compared with those with no history of infection.[69]

Research on persistent symptoms and other conditions after COVID-19 is ongoing, including the National Institutes of Health's RECOVER Initiative, which aims to better characterize the prevalence, characteristics, and pathophysiology of post-acute sequelae of SARS-CoV-2 and inform potential therapeutic strategies.

Considerations in Pregnancy

Minimal data are available on differences or unique characteristics of post-acute sequelae of SARS-CoV-2 among pregnant patients. Persistent symptoms after acute COVID-19 have been reported in pregnant people. In a prospective cohort study of 594 patients (95% of whom were outpatients) with SARS-CoV-2 infection who were pregnant or recently pregnant, 25% had persistent symptoms ≥8 weeks after symptom onset.[70] The most commonly reported persistent symptoms among this cohort were fatigue, shortness of breath, and loss of smell or taste. For pregnant patients and their children, as well as for all patients affected by post-acute sequelae of SARS-CoV-2, more research is needed to understand any unique long-term effects of COVID-19. The RECOVER Initiative plans to enroll and longitudinally follow pregnant patients and their children to better understand any long-term effects of COVID-19.

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Prioritization of Anti-SARS-CoV-2 Therapies for the Treatment of COVID-19 in Nonhospitalized Patients When There Are Logistical Constraints

Last Updated: December 1, 2022

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

When it is necessary to triage patients for receipt of anti-SARS-CoV-2 therapies, the Panel suggests prioritizing individuals with clinical risk factors for severe illness who are unvaccinated or vaccinated but not up to date on their vaccinations and individuals who are not expected to mount an adequate immune response (see Immunocompromising Conditions below).

Prioritization schemes should include a plan for equitable distribution of scarce resources to individuals who may have less knowledge of or access to these therapies. The availability and distribution of recommended therapies should be monitored to ensure that access to products is equitable.

Patient Prioritization for Treatment

The Panel recommends oral **ritonavir-boosted nirmatrelvir (Paxlovid)** as treatment for nonhospitalized patients with mild to moderate COVID-19 who are at high risk of progressing to severe disease **(AIIa)**.

Remdesivir is a recommended option if ritonavir-boosted nirmatrelvir cannot be used. However, some treating facilities may not have the ability to provide a 3-day course of remdesivir intravenous infusions to all eligible patients. In these situations, prioritizing patients who will benefit the most from the therapy becomes necessary. If administration of remdesivir is not feasible, clinicians should review the Panel's latest recommendations for an alternative treatment option.

The prioritization scheme below is based on 4 key elements: age, vaccination status, immune status, and clinical risk factors. For a list of risk factors, see the Centers for Disease Control and Prevention (CDC) webpage Underlying Medical Conditions Associated With Higher Risk for Severe COVID-19. The groups are listed by tier in descending order of priority.

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

Immunocompromising Conditions

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

If remdesivir cannot be provided to all individuals who are moderately to severely immunocompromised and not able to receive ritonavir-boosted nirmatrelvir, the Panel suggests prioritizing patients who are least likely to mount an adequate response to COVID-19 vaccination or SARS-CoV-2 infection and are at risk for severe outcomes, including, but not limited to, patients who:

- Are receiving active treatment for solid tumor and hematologic malignancies.
- Have a hematologic malignancy (e.g., chronic lymphocytic leukemia, non-Hodgkin lymphoma, multiple myeloma, acute leukemia) that has been associated with poor response to COVID-19 vaccines, regardless of the patient's current treatment.
- Received a solid organ or islet transplant and are receiving immunosuppressive therapy.
- Received chimeric antigen receptor T cell (CAR T-cell) therapy or a hematopoietic cell transplant (HCT) and are within 2 years of transplantation or are receiving immunosuppressive therapy.
- Have a moderate or severe primary immunodeficiency (e.g., severe combined immunodeficiency, DiGeorge syndrome, Wiskott-Aldrich syndrome, common variable immunodeficiency disease).
- Have advanced or untreated HIV infection (defined as people with HIV and CD4 T lymphocyte [CD4] cell counts <200 cells/mm^3, a history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV).
- Are receiving active treatment with high-dose corticosteroids (i.e., ≥20 mg prednisone or equivalent per day when administered for ≥2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, or immunosuppressive or immunomodulatory biologic agents (e.g., B cell-depleting agents).

If logistical constraints preclude administration of remdesivir to all prioritized patients, the Panel suggests further prioritizing patients who are more severely immunocompromised and have additional risk factors for severe disease.

Clinical Risk Factors

Some of the most important risk factors for severe COVID-19 include age (risk increases with each decade after age 50),[2] receiving cancer treatment, immunocompromising conditions or receipt of immunosuppressive medications, cardiovascular disease, chronic kidney disease, chronic lung disease, diabetes, obesity (i.e., body mass index ≥30), and pregnancy. For a complete list of risk factors, including information on the relative risk of severe disease, see the CDC webpage Underlying Medical Conditions Associated With Higher Risk for Severe COVID-19. Of note, the likelihood of developing severe COVID-19 increases when a person has multiple comorbidities.[3] For people who are not immunocompromised, vaccination with a primary COVID-19 vaccine series and booster doses dramatically reduces the risk of progression to severe disease.

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

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Clinical Management of Adults Summary

Last Updated: December 28, 2022

Two main processes are thought to drive the pathogenesis of COVID-19. Early in the clinical course, the disease is primarily driven by the replication of SARS-CoV-2. Later in the clinical course, the disease appears to be driven by a dysregulated immune/inflammatory response to SARS-CoV-2 that leads to tissue damage. Based on this understanding, therapies that directly target SARS-CoV-2 are anticipated to 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. Table 2a 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. Table 2b provides guidance on the therapeutic management of hospitalized adult patients according to their disease severity and oxygen requirements.

Table 2a. Therapeutic Management of Nonhospitalized Adults With Mild to Moderate COVID-19 Who Do Not Require Supplemental Oxygen

Patient Disposition	Panel's Recommendations
All Patients	• All patients should be offered symptom management **(AIII)**. • The Panel recommends against the use of **dexamethasone**[a] or **other systemic corticosteroids** in the absence of another indication **(AIIb)**.
Patients Who Are at High Risk of Progressing to Severe COVID-19[b]	*Preferred therapies. Listed in order of preference:* • **Ritonavir-boosted nirmatrelvir (Paxlovid)**[c,d] **(AIIa)** • **Remdesivir**[d,e] **(BIIa)** *Alternative therapy. For use when the preferred therapies are not available, feasible to use, or clinically appropriate:* • **Molnupiravir**[d,f,g] **(CIIa)**
Each recommendation in the Guidelines receives 2 ratings that reflect the strength of the recommendation and the quality of the evidence that supports it. See Guidelines Development for more information.	

[a] There is currently a lack of safety and efficacy data on the use of dexamethasone in outpatients with COVID-19. Using systemic glucocorticoids in outpatients with COVID-19 may cause harm.

[b] For a list of risk factors, see the CDC webpage Underlying Medical Conditions Associated With Higher Risk for Severe COVID-19. When deciding whether to prescribe antiviral treatment to a patient who has been vaccinated, clinicians should be aware of the conditions associated with a high risk of disease progression. These conditions include older age, a prolonged amount of time since the most recent vaccine dose (e.g., >6 months), and a decreased likelihood of an adequate immune response to vaccination due to a moderate to severe immunocompromising condition or the receipt of immunosuppressive medications. The number and severity of risk factors also affects the level of risk.

[c] Ritonavir-boosted nirmatrelvir has significant drug-drug interactions. Clinicians should carefully review a patient's concomitant medications and evaluate potential drug-drug interactions. See Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications for more information.

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

[e] Administration of remdesivir requires an IV infusion once daily for 3 days.

[f] Molnupiravir appears to have lower efficacy than the other options recommended by the Panel. Therefore, it should be considered when the other options are not available, feasible to use, or clinically appropriate.

[g] The Panel **recommends against** the use of **molnupiravir** for the treatment of COVID-19 in pregnant patients unless there are no other options and therapy is clearly indicated **(AIII)**.

Key: CDC = Centers for Disease Control and Prevention; IV = intravenous; the Panel = the COVID-19 Treatment Guidelines Panel

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

Disease Severity	Recommendations for Antiviral or Immunomodulator Therapy		Recommendations for Anticoagulant Therapy
	Clinical Scenario	Recommendation	
Hospitalized for Reasons Other Than COVID-19	Patients with mild to moderate COVID-19 who are at high risk of progressing to severe COVID-19[a]	See Therapeutic Management of Nonhospitalized Adults With COVID-19.	For patients without an indication for therapeutic anticoagulation: • **Prophylactic dose of heparin**, unless contraindicated **(AI)**; **(BIII)** for pregnant patients
Hospitalized but Does Not Require Oxygen Supplementation	All patients	The Panel **recommends against** the use of **dexamethasone (AIIa)** or **other systemic corticosteroids (AIII)** for the treatment of COVID-19.[b]	
	Patients who are at high risk of progressing to severe COVID-19[a]	**Remdesivir**[c] **(BIII)**	
Hospitalized and Requires Conventional Oxygen[d]	Patients who require minimal conventional oxygen	**Remdesivir**[e] **(BIIa)**	For nonpregnant patients with D-dimer levels above the ULN who do not have an increased bleeding risk: • **Therapeutic dose of heparin**[g] **(CIIa)** For other patients: • **Prophylactic dose of heparin**, unless contraindicated **(AI)**; **(BIII)** for pregnant patients
	Most patients	Use **dexamethasone plus remdesivir**[e] **(BIIa)**. If remdesivir cannot be obtained, use **dexamethasone (BI)**.	
	Patients who are receiving dexamethasone and who have rapidly increasing oxygen needs and systemic inflammation	Add **PO baricitinib**[f] or **IV tocilizumab**[f] to 1 of the options above **(BIIa)**.	
Hospitalized and Requires HFNC Oxygen or NIV	Most patients	Promptly start 1 of the following, if not already initiated: • **Dexamethasone plus PO baricitinib**[f] **(AI)** • **Dexamethasone plus IV tocilizumab**[f] **(BIIa)** If **baricitinib**, **tofacitinib**, **tocilizumab**, or **sarilumab** cannot be obtained: • **Dexamethasone**[h] **(AI)** Add **remdesivir** to 1 of the options above in certain patients **(CIIa)**.[i]	For patients without an indication for therapeutic anticoagulation: • **Prophylactic dose of heparin**, unless contraindicated **(AI)**; **(BIII)** for pregnant patients For patients who are started on a therapeutic dose of heparin in a non-ICU setting and then transferred to the ICU, the Panel recommends switching to a **prophylactic dose of heparin**, unless there is another indication for therapeutic anticoagulation **(BIII)**.
Hospitalized and Requires MV or ECMO	Most patients	Promptly start 1 of the following, if not already initiated: • **Dexamethasone plus PO baricitinib**[f] **(BIIa)** • **Dexamethasone plus IV tocilizumab**[f] **(BIIa)** If **baricitinib**, **tofacitinib**, **tocilizumab**, or **sarilumab** cannot be obtained: • **Dexamethasone**[h] **(AI)**	

Each recommendation in the Guidelines receives 2 ratings that reflect the strength of the recommendation and the quality of the evidence that supports it. See Guidelines Development for more information.

[a] For a list of risk factors, see the CDC webpage Underlying Medical Conditions Associated With Higher Risk for Severe COVID-19.

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

[c] Evidence suggests that the benefit of remdesivir is greatest when the drug is given early in the course of COVID-19 (e.g., within 10 days of symptom onset).

[d] Conventional oxygen refers to oxygen supplementation that is not HFNC oxygen, NIV, MV, or ECMO.

[e] If these patients progress to requiring HFNC oxygen, NIV, MV, or ECMO, the full course of remdesivir should still be completed.

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

[g] Contraindications for the use of therapeutic anticoagulation in patients with COVID-19 include a platelet count <50 x 10^9/L, Hgb <8 g/dL, the need for dual antiplatelet therapy, bleeding within the past 30 days that required an ED visit or hospitalization, a history of a bleeding disorder, or an inherited or active acquired bleeding disorder.

[h] If a JAK inhibitor or an anti-IL-6 receptor mAb is not readily available, start dexamethasone while waiting for the additional immunomodulator to be acquired. If neither of the other immunomodulators can be obtained, use dexamethasone alone.

[i] Clinicians may consider adding remdesivir to 1 of the recommended immunomodulator combinations in patients who require HFNC oxygen or NIV, including immunocompromised patients. The Panel **recommends against** the use of remdesivir without immunomodulators in these patients **(AIIa)**.

Key: CDC = Centers for Disease Control and Prevention; ECMO = extracorporeal membrane oxygenation; ED = emergency department; HFNC = high-flow nasal cannula; Hgb = hemoglobin; ICU = intensive care unit; IL = interleukin; IV = intravenous; JAK = Janus kinase; mAb = monoclonal antibody; MV = mechanical ventilation; NIV = noninvasive ventilation; the Panel = the COVID-19 Treatment Guidelines Panel; PO = oral; ULN = upper limit of normal

General Management of Nonhospitalized Adults With Acute COVID-19

Last Updated: September 26, 2022

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 to determine whether they require COVID-19-specific therapy and in-person care **(AIII)**. • Patients who are at high risk of progression to severe COVID-19 may be eligible for pharmacologic therapy. See Therapeutic Management of Nonhospitalized Adults With COVID-19 for specific recommendations. • At a minimum, health care providers should use telehealth to closely follow patients with dyspnea, and in-person monitoring of these patients should be considered **(AIII)**. • Patients with persistent or progressive dyspnea, especially those who have an oxygen saturation measured by pulse oximetry (SpO_2) ≤94% on room air at sea level or have symptoms that suggest high acuity (e.g., chest pain or tightness, dizziness, confusion, other mental status changes), should be referred to a health care provider for an in-person evaluation **(AIII)**. • Clinicians should be aware that using pulse oximeters to measure oxygen saturation has important limitations. Therefore, SpO_2 results should be considered in the context of the patient's clinical condition. See Clinical Spectrum of SARS-CoV-2 Infection for more information.
Each recommendation in the Guidelines receives 2 ratings that reflect the strength of the recommendation and the quality of the evidence that supports it. See Guidelines Development for more information.

Introduction

This section of the Guidelines is intended to provide general information to health care providers who are caring for nonhospitalized adults 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 there are times during the COVID-19 pandemic when the distinction between outpatient and inpatient care may be less clear. 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. In addition, asymptomatic SARS-CoV-2 infection or mild disease may be diagnosed during a patient's hospital admission for a non-COVID-19 condition. 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 emergency department (ED)
- 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.

Data from the United States show that racial and ethnic minorities experience higher rates of COVID-19, hospitalization, and death.[1-5] In addition, inequitable receipt of COVID-19 treatments by race, ethnicity,

and socioeconomic status has been reported.[6-8] The underlying causes of these observed disparities may include barriers to telehealth visits, transportation challenges, inadequate insurance coverage, a lack of primary care providers, and hesitancy about receiving treatment. To reduce COVID-19 treatment disparities, providers must be aware of the problem and provide patient-centered care. All patient groups must have equal access to treatments, regardless of race, ethnicity, or other minoritized status.

Managing Patients With COVID-19 in an Ambulatory Care Setting

Approximately 80% of patients with COVID-19 who are unvaccinated have mild illness that does not require medical intervention or hospitalization,[9] and the proportion is likely higher in patients who are vaccinated. 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.[10]

When managing outpatients with COVID-19, clinicians should provide supportive care, take steps to reduce the risk of SARS-CoV-2 transmission as recommended by the Centers for Disease Control and Prevention (CDC),[11,12] and advise patients on when to seek an in-person evaluation.[13] Supportive care includes managing symptoms (as described below), ensuring that patients are receiving the proper nutrition, and being cognizant of the risks of social isolation, particularly for older adults.[14] Health care providers should identify patients who are at high risk of progression to severe COVID-19. These patients may be candidates for antiviral therapy, including treatment with an anti-SARS-CoV-2 monoclonal antibody (mAb). See Therapeutic Management of Nonhospitalized Adults With COVID-19 for more information.

Older patients and those with chronic medical conditions have a higher risk of hospitalization and death. However, SARS-CoV-2 infection may cause severe disease and death in patients of any age, even in the absence of risk factors. In the care of older adults with COVID-19, factors such as cognitive impairment, frailty, the risk of falls, and polypharmacy should be considered. The decision to monitor a patient in the outpatient setting should be made on a case-by-case basis.

Assessing the Need for In-Person Evaluation

When possible, patients with symptoms of COVID-19 should be triaged via telehealth visits to determine whether they require COVID-19-specific therapy and in-person care **(AIII)**. Outpatient management may include the use of patient self-assessment tools. During the initial triage, clinic staff should determine which patients are eligible to receive supportive care at home and which patients warrant an in-person evaluation.[15] Local emergency medical services, if called by the patient, may also be helpful when deciding whether an in-person evaluation is indicated.

At a minimum, health care providers should use telehealth to closely follow patients with dyspnea, and in-person monitoring of these patients should be considered **(AIII)**. Patients with persistent or progressive dyspnea, especially those who have an oxygen saturation measured by pulse oximetry (SpO_2) ≤94% on room air at sea level or have symptoms that suggest high acuity (e.g., chest pain or tightness, dizziness, confusion, other mental status changes), should be referred to a health care provider for an in-person evaluation **(AIII)**.

Clinicians who use SpO_2 results when assessing patients must be aware of the important limitations of pulse oximeters and conduct assessments in the context of a patient's clinical condition. See Clinical Spectrum of SARS-CoV-2 Infection for more information.

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 people and those with medical conditions associated with an increased risk of progression to severe COVID-19. Individuals who perform the initial triage should use their clinical judgment to determine whether patients require ambulance transport.

In some settings where clinical evaluation is challenged by geography, health care provider home visits may be used to evaluate patients.[16] 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.[14] All outpatients should receive instructions regarding self-care, isolation, and follow-up, and they should be advised to contact a health care provider or a local ED for any worsening symptoms.[17,18] Guidance for implementing home care and isolation for outpatients with COVID-19 is provided by the CDC.

Clinical Considerations When Managing Patients in an Ambulatory Care Setting

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). People who have symptoms compatible with COVID-19 should undergo diagnostic SARS-CoV-2 testing (see Testing for SARS-CoV-2 Infection). Considering other possible etiologies of symptoms is important, including other respiratory viral infections (e.g., influenza), community-acquired pneumonia, congestive heart failure, asthma or chronic obstructive pulmonary disease exacerbations, and streptococcal pharyngitis.

Although mild dyspnea is common, worsening dyspnea and severe chest pain or 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.[19-21] At a minimum, health care providers should use telehealth to closely follow patients with dyspnea, and in-person monitoring of these patients should be considered **(AIII)**. Patients with persistent or progressive dyspnea, especially those who have an SpO_2 ≤94% on room air at sea level or have symptoms that suggest high acuity (e.g., chest pain or tightness, dizziness, confusion, other mental status changes), should be referred to a health care provider for an in-person evaluation **(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 providers if the value is repeatedly below 95% on room air at sea level. Pulse oximetry may not accurately detect hypoxemia, especially in patients who have dark skin pigmentation.[10,22,23]

Not all commercially available pulse oximeters have been cleared by the Food and Drug Administration (FDA). SpO_2 readings obtained through non-FDA-cleared devices, such as over-the-counter sports oximeters or mobile phone applications, lack sufficient accuracy for clinical use.[24,25] Abnormal readings on these devices should be confirmed with an FDA-cleared device or an arterial blood gas analysis. Importantly, SpO_2 readings 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). See Clinical Spectrum of SARS-CoV-2 Infection for more information regarding the limitations of pulse oximetry.

Counseling Regarding the Need for Follow-Up

Health care providers should identify patients who are at high risk of disease progression. These patients may be candidates for antiviral therapy, including treatment with an anti-SARS-CoV-2 mAb (see

Therapeutic Management of Nonhospitalized Adults With COVID-19). 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.

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 facility. Patients with severe disease are typically admitted to the hospital. Rarely, a patient 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.[26] For example, patients who are living in multigenerational households or 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 patients with COVID-19 are not widely available, and community-based solutions for self-care and isolation should be explored.

Treatment with an antiviral agent or anti-SARS-CoV-2 mAb is recommended for patients with mild to moderate COVID-19 who are not on supplemental oxygen and are at high risk of clinical progression (see Therapeutic Management of Nonhospitalized Adults With COVID-19).

In rare 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 patients 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 have provided frequent telemedicine follow-up visits for these patients or a hotline that allows patients to speak with a clinician when necessary. Home resources should be assessed before a patient is discharged from the ED. Outpatients should have a caregiver and access to a device 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.

If a patient is not being admitted to the hospital, the Panel **recommends against** the use of anticoagulants and antiplatelet therapy in the ED for the prevention of venous thromboembolism (VTE) or arterial thrombosis, except in a clinical trial **(AIIa)**. This recommendation does not apply to patients with other indications for antithrombotic therapy. 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 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, although they still require supplemental oxygen. Special consideration may be given to continuing 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.

The Panel **recommends against** routinely continuing VTE prophylaxis after hospital discharge for patients with COVID-19 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 and therapeutics as indicated, 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 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.[27]

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. At this time, there are no changes to fetal monitoring recommendations in the outpatient setting, and fetal surveillance and management should be similar to the fetal surveillance and management used for pregnant patients with medical illness.[28,29] 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.

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Therapeutic Management of Nonhospitalized Adults With COVID-19

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Symptom management should be initiated for all nonhospitalized adults with mild to moderate COVID-19. For adults who are at high risk of progression to severe disease, several antiviral therapeutic options are available to reduce the risk of hospitalization or death. The COVID-19 Treatment Guidelines Panel's (the Panel) recommendations on the use of these drugs for the treatment of COVID-19 are outlined in this section.

The goal of therapeutic management for nonhospitalized patients is to prevent progression to severe disease, hospitalization, or death. Several factors affect the selection of the best treatment option for a specific patient. These factors include the clinical efficacy and availability of the treatment option, the feasibility of administering parenteral medications, the potential for significant drug-drug interactions, the patient's pregnancy status, time from symptom onset, and the in vitro activities of the available products against the currently circulating SARS-CoV-2 variants and subvariants.

Clinical trials supporting the use of the currently available treatment options were largely conducted in individuals who were unvaccinated. Thus, the efficacy of these treatments in patients who have been vaccinated is unclear, although observational data suggest a benefit.[1-6] When deciding whether to prescribe antiviral treatment to a patient who has been vaccinated, clinicians should be aware of the conditions associated with a high risk of disease progression. These conditions include older age, a prolonged amount of time since the most recent vaccine dose (e.g., >6 months), and a decreased likelihood of an adequate immune response to vaccination due to a moderate to severe immunocompromising condition or the receipt of immunosuppressive medications. The number and severity of the risk factors also affects the level of risk.[7]

People who are members of racial and ethnic minority groups have higher rates of hospitalization and death from COVID-19 than people who are White.[8] Disparities in the use of antiviral treatments and anti-SARS-CoV-2 monoclonal antibodies (mAbs) in patients who are not White have been reported; therefore, attention to equitable access is critical.[9,10]

Table 2a outlines the Panel's recommendations for the therapeutic management of nonhospitalized adults with COVID-19. For recommended doses of the agents listed in Table 2a, see Table 4e.

Table 2a. Therapeutic Management of Nonhospitalized Adults With Mild to Moderate COVID-19 Who Do Not Require Supplemental Oxygen

Patient Disposition	Panel's Recommendations
All Patients	• All patients should be offered symptom management **(AIII)**. • The Panel recommends against the use of **dexamethasone**[a] or **other systemic corticosteroids** in the absence of another indication **(AIIb)**.
Patients Who Are at High Risk of Progressing to Severe COVID-19[b]	*Preferred therapies. Listed in order of preference:* • **Ritonavir-boosted nirmatrelvir (Paxlovid)**[c,d] **(AIIa)** • **Remdesivir**[d,e] **(BIIa)** *Alternative therapy. For use when the preferred therapies are not available, feasible to use, or clinically appropriate:* • **Molnupiravir**[d,f,g] **(CIIa)**
Each recommendation in the Guidelines receives 2 ratings that reflect the strength of the recommendation and the quality of the evidence that supports it. See Guidelines Development for more information.	

[a] There is currently a lack of safety and efficacy data on the use of dexamethasone in outpatients with COVID-19. Using systemic glucocorticoids in outpatients with COVID-19 may cause harm.

[b] For a list of risk factors, see the CDC webpage Underlying Medical Conditions Associated With Higher Risk for Severe COVID-19. When deciding whether to prescribe antiviral treatment to a patient who has been vaccinated, clinicians should be aware of the conditions associated with a high risk of disease progression. These conditions include older age, a prolonged amount of time since the most recent vaccine dose (e.g., >6 months), and a decreased likelihood of an adequate immune response to vaccination due to a moderate to severe immunocompromising condition or the receipt of immunosuppressive medications. The number and severity of risk factors also affects the level of risk.

[c] Ritonavir-boosted nirmatrelvir has significant drug-drug interactions. Clinicians should carefully review a patient's concomitant medications and evaluate potential drug-drug interactions. See Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications for more information.

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

[e] Administration of remdesivir requires an IV infusion once daily for 3 days.

[f] Molnupiravir appears to have lower efficacy than the other options recommended by the Panel. Therefore, it should be considered when the other options are not available, feasible to use, or clinically appropriate.

[g] The Panel **recommends against** the use of **molnupiravir** for the treatment of COVID-19 in pregnant patients unless there are no other options and therapy is clearly indicated **(AIII)**.

Key: CDC = Centers for Disease Control and Prevention; IV = intravenous; the Panel = the COVID-19 Treatment Guidelines Panel

Symptom Management

Treatment of symptoms includes using over-the-counter antipyretics, analgesics, or antitussives for fever, headache, myalgias, and cough. 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. When possible, patients with symptoms of COVID-19 should be triaged via telehealth visits to determine whether they require COVID-19-specific therapy and in-person care **(AIII)**.

At a minimum, health care providers should use telehealth to closely follow patients with dyspnea, and in-person monitoring of these patients should be considered **(AIII)**. Patients with persistent or progressive dyspnea, especially those who have an oxygen saturation measured by pulse oximetry ≤94% on room air at sea level or have symptoms that suggest high acuity (e.g., chest pain or tightness, dizziness, confusion, other mental status changes), should be referred to a health care provider for an in-person evaluation **(AIII)**.

Rationale for the Panel's Recommendations

The Panel's recommendations for the antiviral agents that are used to treat nonhospitalized patients with mild to moderate COVID-19 who are at high risk of clinical progression are based on the results of clinical trials. The Panel **recommends against** using anti-SARS-CoV-2 mAbs for the treatment of COVID-19 **(AIII)** because the dominant Omicron subvariants in the United States are not expected to be susceptible to these products. See Anti-SARS-CoV-2 Monoclonal Antibodies for more information.

The Panel favors the use of ritonavir-boosted nirmatrelvir in most high-risk, nonhospitalized patients with mild to moderate COVID-19. When ritonavir-boosted nirmatrelvir is not clinically appropriate (e.g., because of significant drug-drug interactions), the Panel recommends using remdesivir. Ritonavir-boosted nirmatrelvir has high efficacy; has been shown to reduce hospitalization and death when administered to high-risk, unvaccinated, nonhospitalized patients within 5 days of symptom onset;[11] and is an oral medication, whereas remdesivir requires intravenous (IV) administration.

The Panel's recommendation for remdesivir is based on a Phase 3, randomized, placebo-controlled trial that reported high clinical efficacy in high-risk patients with COVID-19 who were unvaccinated.[11,12] However, in some settings, daily IV administration of remdesivir for 3 days may be a logistical challenge.

The Panel recommends **molnupiravir** as a therapeutic option when the other recommended antiviral treatment options are not available, feasible to use, or clinically appropriate **(CIIa)**. Molnupiravir appears to have lower clinical efficacy than the other treatment options, although no randomized studies directly compare these therapies.

Currently, data on the use of combinations of antiviral agents for the treatment of COVID-19 are limited.[13] Clinical trials are needed to determine whether combination therapy has a role in the treatment of COVID-19. The rationale for each of the Panel's recommendations is discussed below.

Strategies for the Use of Ritonavir-Boosted Nirmatrelvir

- Because ritonavir is a strong cytochrome P450 3A4 inhibitor and a P-glycoprotein inhibitor, it may increase blood concentrations of certain concomitant medications and increase the potential for serious drug toxicities.
- Many drug-drug interactions between ritonavir-boosted nirmatrelvir and concomitant medications **can be safely managed** (e.g., with certain statins, calcium channel blockers, or direct oral anticoagulants). If a significant drug-drug interaction is identified, prescribers should consider consulting with a pharmacist. The following resources are available to assist in identifying and managing drug-drug interactions:
  - Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications
  - The Liverpool COVID-19 Drug Interactions website
  - The University of Waterloo/University of Toronto drug interaction guide
  - The Food and Drug Administration (FDA) Emergency Use Authorization (EUA) fact sheet and checklist for ritonavir-boosted nirmatrelvir
- The use of ritonavir-boosted nirmatrelvir may be challenging in patients with severe renal impairment and in patients receiving certain transplant-related immunosuppressants or chemotherapy.
  - The EUA states that until more data are available, ritonavir-boosted nirmatrelvir is not recommended in patients with an estimated glomerular filtration rate (eGFR) of <30 mL/min.[14] Although data on dose adjustments are limited, some groups have proposed adjustments for patients with an eGFR <30 mL/min or for patients receiving hemodialysis.[15-19]
  - The decision to prescribe ritonavir-boosted nirmatrelvir to patients receiving calcineurin and mammalian target of rapamycin inhibitors should always be made in consultation with the patient's specialist providers. Ritonavir-boosted nirmatrelvir may be prescribed safely to select patients if an expert in managing the interaction is available and close therapeutic drug monitoring is logistically feasible. Otherwise, an alternative therapy for COVID-19 should be considered. See the American Society of Transplantation statement for additional information.
  - Interactions between ritonavir-boosted nirmatrelvir and chemotherapeutic agents should also be managed in consultation with the patient's specialist providers. For guidance on managing these interactions, refer to the FDA EUA fact sheet and the prescribing information for the chemotherapeutic agent. The University Health Network/Kingston Health Sciences Centre

provides an additional resource for evaluating drug-drug interactions between ritonavir-boosted nirmatrelvir and chemotherapeutic agents.

Strategies for the Use of Remdesivir

- If remdesivir is to be used in patients with renal impairment, clinicians may prefer to use the lyophilized powder formulation of remdesivir, which contains less sulfobutylether beta-cyclodextrin sodium than the solution formulation. The FDA product label for remdesivir does not recommend its use in patients with an eGFR of <30 mL/min. However, some data suggest that remdesivir can be used in patients with an eGFR of <30 mL/min if the potential benefits outweigh the risks.[20-23] See Remdesivir for more information.
- Advanced planning (e.g., reserving infusion slots, identifying alternative infusion sites) may be needed to increase access to IV remdesivir.
- IV remdesivir can be administered in skilled nursing facilities, home health care settings, and outpatient facilities such as infusion centers.
- If treating facilities cannot provide a 3-day course of remdesivir IV infusions to all eligible patients, prioritizing patients who will benefit the most from the therapy becomes necessary (see the prioritization scheme below).

The prioritization scheme below is based on 4 key elements: age, vaccination status, immune status, and clinical risk factors. For a list of risk factors, see the Centers for Disease Control and Prevention webpage Underlying Medical Conditions Associated With Higher Risk for Severe COVID-19. The groups are listed by tier in descending order of priority.

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

See Prioritization of Anti-SARS-CoV-2 Therapies for the Treatment of COVID-19 in Nonhospitalized Patients When There Are Logistical Constraints for more information.

Additional Information on Ritonavir-Boosted Nirmatrelvir

Nirmatrelvir is an orally bioavailable protease inhibitor that is active against M^{PRO}, a viral protease that plays an essential role in viral replication.[24] The FDA issued an EUA for ritonavir-boosted nirmatrelvir for the treatment of mild to moderate COVID-19 in nonhospitalized adults and pediatric patients aged ≥12 years and weighing ≥40 kg who are at high risk of disease progression.[14]

- Patients should complete the 5-day treatment course of ritonavir-boosted nirmatrelvir, which was shown to be efficacious in the pivotal clinical trial.[11]
- If a patient requires hospitalization after starting treatment, the full 5-day treatment course of ritonavir-boosted nirmatrelvir should be completed unless there are drug-drug interactions that

preclude its use.

- For considerations in pregnancy, see Ritonavir-Boosted Nirmatrelvir (Paxlovid).

In the EPIC-HR trial, ritonavir-boosted nirmatrelvir reduced the risk of hospitalization or death by 88% compared to placebo in unvaccinated, nonhospitalized adults with laboratory-confirmed SARS-CoV-2 infection.[11,14] This efficacy is comparable to the efficacies reported in similar patient populations for remdesivir (87% relative reduction)[12] and greater than the efficacy reported for molnupiravir in this setting (31% relative reduction).[25]

Ritonavir-boosted nirmatrelvir is expected to be active against all Omicron subvariants, although clinical efficacy data are lacking.[26-28] Because ritonavir-boosted nirmatrelvir has the potential for significant drug-drug interactions with concomitant medications, this regimen may not be the optimal choice for all patients (see Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir [Paxlovid] and Concomitant Medications). However, because ritonavir-boosted nirmatrelvir is the only highly effective oral antiviral available for the treatment of COVID-19, drug-drug interactions that can be safely managed should not preclude the use of this medication.

SARS-CoV-2 Viral Rebound

Observational studies and results from the EPIC-HR trial have described SARS-CoV-2 viral rebound and the recurrence of COVID-19 symptoms in some patients who have completed treatment with ritonavir-boosted nirmatrelvir.[14,29-31] The frequency, mechanism, and clinical implications of these events are unclear. Viral rebound and the recurrence of COVID-19 symptoms can also occur in the absence of treatment with ritonavir-boosted nirmatrelvir.[32,33] To date, recurrence of symptoms following the use of ritonavir-boosted nirmatrelvir has not been associated with progression to severe COVID-19 and should not be a reason to avoid its use.[32,34,35] The current FDA EUA does not authorize treatment courses of ritonavir-boosted nirmatrelvir that are longer than 5 days, and there are insufficient data on the efficacy of administering a second course.[35]

For more information, see Ritonavir-Boosted Nirmatrelvir (Paxlovid).

Additional Information on Remdesivir

Remdesivir is a nucleotide prodrug of an adenosine analog that inhibits SARS-CoV-2 replication. It is approved by the FDA for the treatment of COVID-19 in adults and children aged ≥28 days and weighing ≥3 kg who are hospitalized with COVID-19 and for those with mild to moderate COVID-19 who are not hospitalized and are at high risk of progression to severe disease. In the PINETREE trial, nonhospitalized patients with mild to moderate COVID-19 who were unvaccinated and at high risk of progressing to severe disease received 3 days of IV remdesivir or placebo. Use of remdesivir resulted in an 87% relative reduction in the risk of hospitalization or death.[12] Remdesivir has demonstrated activity in vitro and in animal studies against the Omicron variant and its subvariants.[36-38]

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

For more information, including considerations in pregnancy, see Remdesivir.

Additional Information on Molnupiravir

Molnupiravir is the oral prodrug of beta-D-N4-hydroxycytidine, a ribonucleoside that has exhibited antiviral activity against SARS-CoV-2 in vitro and in clinical trials.[39-41] The FDA issued an EUA for molnupiravir for the treatment of mild to moderate COVID-19 in nonhospitalized patients aged ≥18

years who are at high risk of disease progression and for whom alternative treatment options are not accessible or clinically appropriate. In vitro and animal studies have demonstrated that molnupiravir is active against Omicron subvariants.[28,38,41,42]

Molnupiravir is a mutagenic ribonucleoside antiviral agent, and there is a theoretical risk that the drug will be metabolized by the human host cell and incorporated into the host DNA, leading to mutations. The available genotoxicity data and the 5-day duration of treatment led the FDA to conclude that molnupiravir has a low risk for genotoxicity.[14]

- The Panel **recommends against** the use of **molnupiravir** for the treatment of COVID-19 in pregnant patients unless there are no other options and therapy is clearly indicated **(AIII)**.
- People who engage in sexual activity that may result in conception should use effective contraception during and following treatment with molnupiravir. For more details, see Molnupiravir.

The MOVe-OUT trial enrolled nonhospitalized adults who were unvaccinated and at high risk of progression to severe disease in the pre-Omicron era and reported that molnupiravir reduced the rate of hospitalization or death by 31% compared to placebo.[14,25] In a secondary analysis of MOVe-OUT trial data, patients who received molnupiravir and progressed to hospitalization were less likely to need respiratory interventions than patients who received placebo and progressed to hospitalization.[43] Although the different COVID-19 treatment options have not been directly compared in clinical trials, the Panel recommends using molnupiravir as an alternative therapy when ritonavir-boosted nirmatrelvir and remdesivir are not available, feasible to use, or clinically appropriate, because molnupiravir appears to have lower efficacy than these other options.

Fetal toxicity has been reported in animal studies of molnupiravir.[14] However, when other therapies are not available, pregnant patients with COVID-19 who are at high risk of progressing to severe disease may reasonably choose molnupiravir after being fully informed of the risks, particularly if they are beyond the time of embryogenesis (i.e., >10 weeks' gestation). See Special Considerations in Pregnancy for more information.

For more information, see Molnupiravir.

Immunomodulators

The Panel **recommends against** the use of **dexamethasone** or **other systemic corticosteroids** to treat outpatients with mild to moderate COVID-19 who do not require hospitalization or supplemental oxygen **(AIIb)**. Patients with COVID-19 who are receiving **dexamethasone** or **another corticosteroid** for an underlying condition should continue this therapy as directed by their health care provider **(AIII)**.

Medicare and FDA data show a significant increase in the number of prescriptions for systemic corticosteroids among nonhospitalized patients with COVID-19[44] despite a lack of safety and efficacy data on the use of systemic corticosteroids in this setting. Systemic glucocorticoids may cause harm in nonhospitalized patients with COVID-19. Results from 1 randomized controlled trial and 1 observational cohort study did not demonstrate a clinical benefit of dexamethasone among hospitalized patients who did not require supplemental oxygen,[45] and dexamethasone may potentially cause harm in these patients.[46]

In the RECOVERY trial, the use of dexamethasone had no effect on mortality among hospitalized patients with COVID-19 who did not require supplemental oxygen (rate ratio 1.19; 95% CI, 0.91–1.55).[45] A large observational study of patients at Veterans Affairs hospitals reported no survival benefit for dexamethasone among patients with COVID-19 who did not require supplemental oxygen. Instead,

these patients had an increased risk of 90-day mortality (HR 1.76; 95% CI, 1.47–2.12).[46] However, hospitalized patients with COVID-19 are likely to have an increased risk of mortality compared to nonhospitalized patients, which is a limitation of observational trial data.

Other Agents That Have Been Studied or Are Under Investigation

- The Panel **recommends against** the use of **chloroquine** or **hydroxychloroquine** with or without **azithromycin (AIIa)**, **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. Although none of these are currently recommended, additional information can be found in sections of the guidelines that address:
  - Drugs such as colchicine, fluvoxamine, ivermectin, inhaled corticosteroids, and metformin
  - Supplements such as vitamin C, vitamin D, and zinc
- The Panel **recommends against** the use of anticoagulants and antiplatelet therapy for the prevention of venous thromboembolism or arterial thrombosis unless the patient has other indications for the therapy or is participating in a clinical trial **(AIIa)**. For more information, see Antithrombotic Therapy in Patients With COVID-19.

Concomitant Medication Management

In general, a patient's usual medication and/or supplement regimen should be continued after the diagnosis of COVID-19 (see Considerations for Using Concomitant Medications in Patients With COVID-19). Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), statin therapy, nonsteroidal anti-inflammatory drugs, and oral, inhaled, and intranasal corticosteroids that are prescribed for comorbid conditions should be continued as directed (**AIIa** for ACE inhibitors and ARBs; **AIII** for other medications). Patients should be advised to avoid the use of nebulized medications in the presence of others to avoid potential aerosolization of SARS-CoV-2.[47] 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 or an expert in the subspecialty should be consulted about the risks and benefits 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 (see Special Considerations in People Who Are Immunocompromised).

Before prescribing ritonavir-boosted nirmatrelvir, **clinicians should carefully review the patient's concomitant medications**, including over-the-counter medications and herbal supplements, to evaluate potential drug-drug interactions.

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Therapeutic Management of Hospitalized Adults With COVID-19

Last Updated: August 8, 2022

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

Disease Severity	Recommendations for Antiviral or Immunomodulator Therapy		Recommendations for Anticoagulant Therapy
	Clinical Scenario	Recommendation	
Hospitalized for Reasons Other Than COVID-19	Patients with mild to moderate COVID-19 who are at high risk of progressing to severe COVID-19[a]	See Therapeutic Management of Nonhospitalized Adults With COVID-19.	For patients without an indication for therapeutic anticoagulation: • **Prophylactic dose of heparin**, unless contraindicated **(AI)**; **(BIII)** for pregnant patients
Hospitalized but Does Not Require Oxygen Supplementation	All patients	The Panel **recommends against** the use of **dexamethasone (AIIa)** or **other systemic corticosteroids (AIII)** for the treatment of COVID-19.[b]	
	Patients who are at high risk of progressing to severe COVID-19[a]	**Remdesivir**[c] **(BIII)**	
Hospitalized and Requires Conventional Oxygen[d]	Patients who require minimal conventional oxygen	**Remdesivir**[e] **(BIIa)**	For nonpregnant patients with D-dimer levels above the ULN who do not have an increased bleeding risk: • **Therapeutic dose of heparin**[g] **(CIIa)** For other patients: • **Prophylactic dose of heparin**, unless contraindicated **(AI)**; **(BIII)** for pregnant patients
	Most patients	Use **dexamethasone plus remdesivir**[e] **(BIIa)**. If remdesivir cannot be obtained, use **dexamethasone (BI)**.	
	Patients who are receiving dexamethasone and who have rapidly increasing oxygen needs and systemic inflammation	Add **PO baricitinib**[f] or **IV tocilizumab**[f] to 1 of the options above **(BIIa)**.	
Hospitalized and Requires HFNC Oxygen or NIV	Most patients	Promptly start 1 of the following, if not already initiated: • **Dexamethasone plus PO baricitinib**[f] **(AI)** • **Dexamethasone plus IV tocilizumab**[f] **(BIIa)** If **baricitinib**, **tofacitinib**, **tocilizumab**, or **sarilumab** cannot be obtained: • **Dexamethasone**[h] **(AI)** Add **remdesivir** to 1 of the options above in certain patients **(CIIa)**.[i]	For patients without an indication for therapeutic anticoagulation: • **Prophylactic dose of heparin**, unless contraindicated **(AI)**; **(BIII)** for pregnant patients For patients who are started on a therapeutic dose of heparin in a non-ICU setting and then transferred to the ICU, the Panel recommends switching to a **prophylactic dose of heparin**, unless there is another indication for therapeutic anticoagulation **(BIII)**.
Hospitalized and Requires MV or ECMO	Most patients	Promptly start 1 of the following, if not already initiated: • **Dexamethasone plus PO baricitinib**[f] **(BIIa)** • **Dexamethasone plus IV tocilizumab**[f] **(BIIa)** If **baricitinib**, **tofacitinib**, **tocilizumab**, or **sarilumab** cannot be obtained: • **Dexamethasone**[h] **(AI)**	

Each recommendation in the Guidelines receives 2 ratings that reflect the strength of the recommendation and the quality of the evidence that supports it. See Guidelines Development for more information.

[a] For a list of risk factors, see the CDC webpage Underlying Medical Conditions Associated With Higher Risk for Severe COVID-19.

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

[c] Evidence suggests that the benefit of remdesivir is greatest when the drug is given early in the course of COVID-19 (e.g., within 10 days of symptom onset).

[d] Conventional oxygen refers to oxygen supplementation that is not HFNC oxygen, NIV, MV, or ECMO.

[e] If these patients progress to requiring HFNC oxygen, NIV, MV, or ECMO, the full course of remdesivir should still be completed.

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

[g] Contraindications for the use of therapeutic anticoagulation in patients with COVID-19 include a platelet count <50 x 10^9/L, Hgb <8 g/dL, the need for dual antiplatelet therapy, bleeding within the past 30 days that required an ED visit or hospitalization, a history of a bleeding disorder, or an inherited or active acquired bleeding disorder.

[h] If a JAK inhibitor or an anti-IL-6 receptor mAb is not readily available, start dexamethasone while waiting for the additional immunomodulator to be acquired. If neither of the other immunomodulators can be obtained, use dexamethasone alone.

[i] Clinicians may consider adding remdesivir to 1 of the recommended immunomodulator combinations in patients who require HFNC oxygen or NIV, including immunocompromised patients. The Panel **recommends against** the use of remdesivir without immunomodulators in these patients **(AIIa)**.

Key: CDC = Centers for Disease Control and Prevention; ECMO = extracorporeal membrane oxygenation; ED = emergency department; HFNC = high-flow nasal cannula; Hgb = hemoglobin; ICU = intensive care unit; IL = interleukin; IV = intravenous; JAK = Janus kinase; mAb = monoclonal antibody; MV = mechanical ventilation; NIV = noninvasive ventilation; the Panel = the COVID-19 Treatment Guidelines Panel; PO = oral; ULN = upper limit of normal

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 also driven by a dysregulated immune/inflammatory response to SARS-CoV-2 infection that may lead to further tissue damage and thrombosis. Based on this understanding, therapies that directly target SARS-CoV-2 are anticipated to have the greatest effect early in the course of the disease, whereas immunosuppressive, anti-inflammatory, and antithrombotic therapies are likely to be more beneficial after COVID-19 has progressed to stages characterized by hypoxemia and endothelial dysfunction.

Below is a summary of the rationale for the COVID-19 Treatment Guidelines Panel's (the Panel) recommendations on the therapeutic management of hospitalized patients with COVID-19. For dosing information for each of the recommended drugs, please refer to Table 2c below. For detailed information regarding the therapies and evidence from clinical trials that support the Panel's recommendations, please refer to the specific drug pages and clinical data tables.

Patients Who Are Hospitalized for Reasons Other Than COVID-19 and Who Do Not Require Supplemental Oxygen

Hospitalized patients with COVID-19 who do not require supplemental oxygen are a heterogeneous population. Some patients may be hospitalized for reasons other than COVID-19 but may also have mild to moderate COVID-19 (see Clinical Spectrum of SARS-CoV-2 Infection). In these cases, patients who are at high risk of progressing to severe COVID-19 may benefit from antiviral therapy.

Remdesivir has been approved by the Food and Drug Administration (FDA) for the treatment of COVID-19 in adult and pediatric patients aged ≥12 years and weighing ≥40 kg, and several other therapies have received FDA Emergency Use Authorizations for use in patients with mild to moderate COVID-19 who are at high risk of progressing to severe disease. These therapies can be used in hospitalized patients who qualify for therapy if they were admitted to the hospital for a diagnosis other than COVID-19. The Panel's recommendations for these patients are the same as those for nonhospitalized patients (see Therapeutic Management of Nonhospitalized Adults With COVID-19).

Patients Who Are Hospitalized for COVID-19 and Who Do Not Require Supplemental Oxygen

Recommendations

- The Panel recommends using **remdesivir** for the treatment of COVID-19 in patients who do not require supplemental oxygen and who are at high risk of progressing to severe disease **(BIII)**.
- Remdesivir should be administered for 5 days or until hospital discharge, whichever comes first.

The rationale for using remdesivir in this population is based on several lines of evidence. In a trial conducted predominantly among hospitalized patients with COVID-19 who were not receiving supplemental oxygen at enrollment, a 5-day course of remdesivir was associated with greater clinical improvement, when compared with standard of care.[1] Evidence from the PINETREE trial also suggests that early therapy reduces the risk of progression, although that study was performed in high-risk, unvaccinated, nonhospitalized patients with ≤7 days of symptoms.

Other studies have not shown a clinical benefit of remdesivir in this group of hospitalized patients with COVID-19. In ACTT-1, remdesivir showed no significant benefit in hospitalized patients with mild to moderate disease. However, only 13% of the study population did not require supplemental oxygen. In the large Solidarity trial, the use of remdesivir was not associated with a survival benefit among the subset of hospitalized patients who did not require supplemental oxygen. See Table 4a for more information.

The aggregate data on using remdesivir to treat this population show a faster time to recovery in patients who received remdesivir but no clear evidence of a survival benefit. Given the impact on reducing progression, the Panel finds that the available data support a recommendation for using remdesivir in hospitalized patients with COVID-19 who are at risk of progressing to severe disease. For information on medical conditions that confer high risk, see the Centers for Disease Control and Prevention webpage People With Certain Medical Conditions.

Recommendation

- The Panel **recommends against** the use of **dexamethasone (AIIa)** or **other systemic corticosteroids (AIII)** for the treatment of COVID-19 in patients who do not require supplemental oxygen.

In the RECOVERY trial, no survival benefit was observed for dexamethasone among the subset of patients with COVID-19 who did not require supplemental oxygen at enrollment.[2] In an observational cohort study of U.S. veterans, the use of dexamethasone was associated with higher mortality in hospitalized patients with COVID-19 who did not require supplemental oxygen.[3]

There are no data to support the use of other systemic corticosteroids in hospitalized patients with COVID-19. However, patients who are receiving corticosteroid treatment for an underlying condition should continue to receive corticosteroids. See Table 5a for more information.

Patients Who Require Conventional Oxygen

Patients with COVID-19 who require conventional oxygen (i.e., those who do not require high-flow nasal cannula [HFNC] oxygen, noninvasive ventilation [NIV], or mechanical ventilation) are a heterogeneous population. Although the oxygen requirement qualifies all these patients as having severe disease, some of these patients will improve after a short period with or without treatment; others will develop progressive disease. There is no consensus on which clinical or laboratory parameters should be used to determine a patient's risk of progression and guide therapy.

Recommendation

- For patients with COVID-19 who only require minimal conventional oxygen, the Panel recommends using **remdesivir** without dexamethasone **(BIIa)**.

In these patients, the hyperinflammatory state for which corticosteroids might be most beneficial may not yet be present or fully developed. In a subgroup analysis during the ACTT-1 trial, remdesivir significantly reduced the time to clinical recovery and significantly reduced mortality among the subset of patients who were receiving conventional oxygen at enrollment.[4] Evidence from ACTT-1 suggests that remdesivir will have its greatest benefit when administered early in the clinical course of COVID-19 (e.g., within 10 days of symptom onset). See Table 4a for more information.

Recommendations

- For most patients with COVID-19 who require conventional oxygen, the Panel recommends using **dexamethasone plus remdesivir (BIIa)**.
- If dexamethasone is not available, an equivalent dose of another corticosteroid (e.g., **prednisone**, **methylprednisolone**, or **hydrocortisone**) may be used **(BIII)**.

The results of several studies suggest that the use of remdesivir plus dexamethasone improves clinical outcomes among hospitalized patients with COVID-19. In the CATCO trial, in which 87% of patients received corticosteroids and 54% were on conventional oxygen, remdesivir significantly reduced the need for mechanical ventilation among the subset of patients who did not require mechanical ventilation at enrollment, when compared with standard of care.[5] In the Solidarity trial, in which approximately two-thirds of the patients received corticosteroids, remdesivir significantly reduced mortality among the subset of patients who were receiving conventional or HFNC oxygen at enrollment.[6] See Table 4a for more information.

Recommendation

- If remdesivir is not available, the Panel recommends using **dexamethasone alone** in patients with COVID-19 who require conventional oxygen **(BI)**.

In the RECOVERY trial, dexamethasone significantly reduced mortality among the subset of patients who were receiving oxygen (defined as receiving oxygen supplementation but not mechanical ventilation or extracorporeal membrane oxygenation [ECMO]) at enrollment.[2] Remdesivir was administered to <1% of the study participants. Results for patients who were only receiving conventional oxygen at enrollment were not available. See Table 5a for more information.

Recommendation

- The Panel recommends adding a second immunomodulatory drug (e.g., **baricitinib** or **tocilizumab**) to dexamethasone in patients who have rapidly increasing oxygen needs and systemic inflammation **(BIIa)**.

Several large randomized trials evaluated the use of interleukin (IL)-6 inhibitors (e.g., tocilizumab, sarilumab) or Janus kinase (JAK) inhibitors (e.g., baricitinib, tofacitinib) with or without corticosteroids in patients with COVID-19.[7-11] These studies included some patients who required conventional oxygen only, as well as those with increasing oxygen needs and/or elevated levels of inflammatory markers. Subgroup analyses in these trials have not clearly defined which patients in this heterogeneous group are most likely to benefit from adding another immunomodulator to their corticosteroid regimens. Nonetheless, some trials suggest that adding a second immunomodulator to dexamethasone provides benefits to patients who require conventional oxygen, especially those with rapidly increasing oxygen requirements and systemic inflammation. Because there are no studies that directly compare the use of baricitinib and tocilizumab as treatments for COVID-19, the Panel has insufficient evidence to recommend 1 drug over the other.

Use of Anticoagulants

- The Panel recommends using a **therapeutic dose of heparin** for nonpregnant patients with D-dimer levels above the upper limit of normal who require conventional oxygen and who do not have an increased bleeding risk **(CIIa)**.
- Patients who do not meet the criteria for therapeutic heparin noted above, including pregnant individuals, should receive a **prophylactic dose of heparin**, unless this drug is contraindicated **(AI)**; **(BIII)** for pregnant patients.

The Panel's recommendations for the use of heparin are based on data from 3 open-label randomized controlled trials that compared the use of therapeutic doses of heparin to prophylactic or intermediate doses of heparin in hospitalized patients who did not require intensive care unit (ICU)-level care. The multiplatform ATTACC/ACTIV-4a/REMAP-CAP trial reported more organ support-free days for patients in the therapeutic heparin arm than in the usual care arm, but there was no difference between the arms in mortality or length of hospitalization.[12] The RAPID trial compared a therapeutic dose of heparin to a prophylactic dose in hospitalized patients with moderate COVID-19. There was no statistically significant difference between the arms in the occurrence of the primary endpoint (which was a composite endpoint of ICU admission and initiation of NIV or mechanical ventilation), but the therapeutic dose of heparin reduced 28-day mortality.[13] In the HEP-COVID trial, venous thromboembolism (VTE), arterial thromboembolism, and death by Day 30 occurred significantly less frequently in patients who received a therapeutic dose of heparin than in those who received a prophylactic dose of heparin, but there was no difference in mortality by Day 30 between the arms.[14]

Patients Who Require High-Flow Nasal Cannula Oxygen or Noninvasive Ventilation

In these patients, systemic inflammation contributes to hypoxemia as the predominant clinical feature, and patients benefit from a second immunomodulator in addition to dexamethasone. There is no consensus on which clinical or laboratory parameters reliably predict the risk of death or progression to mechanical ventilation.

The available evidence suggests that the benefits of adding baricitinib or tocilizumab to dexamethasone treatment outweigh the potential risks in patients with COVID-19 who require HFNC oxygen, NIV, mechanical ventilation, or ECMO. Although the combination of dexamethasone and secondary immunomodulating medications may increase the risk of opportunistic infections or the risk of reactivating latent infections, there are insufficient data to make recommendations about initiating prophylaxis against these infections.

Recommendations

- For most patients, the Panel recommends using 1 of the following combinations of immunomodulators:
  - **Dexamethasone plus oral (PO) baricitinib (AI)**; *or*
  - **Dexamethasone plus intravenous (IV) tocilizumab (BIIa)**

Several large randomized controlled trials have demonstrated that these patients benefit from combining dexamethasone with an additional immunomodulator, such as an IL-6 inhibitor (e.g., tocilizumab, sarilumab) or a JAK inhibitor (e.g., baricitinib, tofacitinib). See Table 5c and Table 5d for more information.

The use of baricitinib plus dexamethasone was associated with a survival benefit among hospitalized patients with COVID-19 in the RECOVERY trial. The treatment effect was most pronounced among patients who were receiving HFNC oxygen or NIV.[11] The COV-BARRIER trial also demonstrated a survival benefit of baricitinib that was most pronounced among patients who were receiving HFNC oxygen or NIV.[10] Data from the ACTT-2[9] and ACTT-4[15] trials support the overall safety of baricitinib and the potential for a clinical benefit, but neither trial studied baricitinib in combination with dexamethasone as the standard of care.

In the REMAP-CAP trial, the use of tocilizumab in combination with corticosteroids reduced in-hospital mortality in patients with rapid respiratory decompensation who were admitted to the ICU.[16] Similar results were reported during the RECOVERY trial.[7] However, patients were only selected for randomization into the tocilizumab arm during the RECOVERY trial if they had oxygen saturation <92% on room air and C-reactive protein levels ≥75 mg/L. These factors put them at higher risk of clinical progression. Both REMAP-CAP and RECOVERY evaluated the efficacy of adding tocilizumab to standard care; in both cases, standard care included dexamethasone therapy. Other randomized trials that have evaluated the use of tocilizumab have demonstrated mixed results, including a lack of benefit when tocilizumab was administered without dexamethasone as part of standard care.

Combinations of 3 immunomodulators (e.g., dexamethasone plus baricitinib plus tocilizumab) have not been studied in clinical trials. Although some patients in the baricitinib arm of the RECOVERY trial also received tocilizumab, data from the study are insufficient to issue a recommendation. When both agents are used, a potential for additive risk of secondary infections remains.[11]

In summary, the clinical trials data cited above informed the Panel's recommendations for adding a second immunomodulator to dexamethasone in hospitalized patients who require HFNC oxygen or NIV. The quality of the evidence and the totality of the data support a stronger recommendation for baricitinib than tocilizumab. See Table 5c and Table 5d for more information.

Recommendation

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

When neither baricitinib nor tocilizumab is available or feasible to use, the JAK inhibitor tofacitinib or the IL-6 inhibitor sarilumab may be used as alternative agents for baricitinib or tocilizumab, respectively. Tofacitinib decreased the risk for respiratory failure or death in the STOP-COVID trial,[17] and sarilumab reduced mortality and the duration of organ support to the same degree as tocilizumab in the REMAP-CAP trial.[8]

Recommendation

- The Panel recommends using **dexamethasone alone** if baricitinib, tofacitinib, tocilizumab, or sarilumab cannot be obtained **(AI)**.

Significant effort should be made to obtain baricitinib, tofacitinib, tocilizumab, or sarilumab. Dexamethasone should be initiated immediately, without waiting until the second immunomodulator can be acquired. Dexamethasone was used as a single-agent immunomodulatory strategy in the RECOVERY trial and demonstrated a survival benefit among patients who required supplemental oxygen.[2] At the time of the trial, the treatment effect for dexamethasone could not be evaluated separately for those who required conventional oxygen and those who required HFNC oxygen or NIV (see Corticosteroids).

Recommendation

- For hospitalized patients who require HFNC oxygen or NIV and have certain medical conditions, the Panel recommends adding **remdesivir** to 1 of the recommended immunomodulator combinations **(CIIa)**.

Although clinical trial data have not established a clear benefit of using remdesivir in patients who require HFNC oxygen or NIV, the Panel's recommendation reflects the balance of 2 factors. First, given that these patients are routinely treated with 2 immunomodulators to prevent or mitigate inflammatory-mediated injury, these treatments may impair the patient's antiviral response, and directly treating the virus with remdesivir may help improve outcomes. In this context, some Panel members would add remdesivir to treatments for immunocompromised patients who require HFNC oxygen or NIV. In addition, clinicians may extend the course of remdesivir beyond 5 days in this population based on clinical response. In the Solidarity trial, remdesivir had a modest but statistically significant effect on reducing the risk of death or progression to mechanical ventilation; however, these effects could not be evaluated separately for patients who required conventional oxygen supplementation and those who required HFNC oxygen or NIV.[18] See Table 4a for more information.

Recommendation

- The Panel **recommends against** the use of remdesivir without immunomodulators in hospitalized patients who require HFNC oxygen or NIV **(AIIa)**.

In the ACTT-1 trial, hospitalized patients with COVID-19 received remdesivir or placebo without immunomodulators. In the subgroup of 193 patients who required high-flow oxygen or NIV at enrollment, there was no difference in time to recovery between patients in the remdesivir arm and patients in the placebo arm (recovery rate ratio 1.09; 95% CI, 0.76–1.57). A post hoc analysis did not show a survival benefit for remdesivir at Day 29 (HR 1.02; 95% CI, 0.54–1.91).[4]

The Panel recommends against using remdesivir without immunomodulators in patients who require HFNC oxygen or NIV because there is uncertainty regarding whether using remdesivir by itself confers a clinical benefit in this subgroup. Patients who are taking remdesivir and then progress to requiring HFNC oxygen or NIV should complete the course of remdesivir. If these patients are not already receiving 1 of the recommended immunomodulator combinations as part of their treatment, they should initiate immunomodulatory therapy.

Use of Anticoagulants

- For patients without an indication for therapeutic anticoagulation, the Panel recommends using a **prophylactic dose of heparin** as VTE prophylaxis, unless a contraindication exists **(AI)**; **(BIII)** for pregnant patients.

- For patients who are started on a therapeutic dose of heparin in a non-ICU setting for the management of COVID-19 and then transferred to the ICU, the Panel recommends switching from the therapeutic dose to a **prophylactic dose of heparin**, unless VTE is confirmed **(BIII)**.
- The Panel **recommends against** the use of an **intermediate dose** (e.g., enoxaparin 1 mg/kg once daily) or a **therapeutic dose of anticoagulation** for VTE prophylaxis, except in a clinical trial **(BI)**.

The INSPIRATION trial compared the use of intermediate doses of anticoagulation to prophylactic doses in adults who were admitted to the ICU with COVID-19. There was no difference between the arms in the incidence of VTE, the incidence of arterial thrombosis, the need for ECMO, or all-cause mortality.[19] The multiplatform randomized controlled trial REMAP-CAP/ACTIV-4a/ATTACC compared the effectiveness of a therapeutic dose of heparin to standard care in critically ill patients with COVID-19. The study did not show an increase in the number of organ support-free days or the probability of survival to hospital discharge among patients who received therapeutic doses of anticoagulation.[20] See Antithrombotic Therapy in Patients With COVID-19 for more information.

Patients Who Require Mechanical Ventilation or Extracorporeal Membrane Oxygenation

Recommendation

- The Panel recommends initiating **dexamethasone plus PO baricitinib (BIIa)** or **dexamethasone plus IV tocilizumab (BIIa)** if not already initiated in patients with COVID-19 who require mechanical ventilation or ECMO.

Clinical trials that have evaluated combining IL-6 inhibitors and JAK inhibitors with corticosteroids for the treatment of patients with COVID-19 provide the most robust evidence for the Panel's recommendations.

Clinical trials of tocilizumab have reported an overall survival benefit in patients with hypoxemia and signs of systemic inflammation (RECOVERY)[7] and in patients who are critically ill and require organ support (REMAP-CAP).[16] Although these studies included patients who were receiving mechanical ventilation at randomization, the studies were not specifically powered to assess the effectiveness of IL-6 inhibitors in these patients. Other studies of tocilizumab in critically ill patients did not find a survival benefit, although the time between initiation of organ support in the ICU and study enrollment differed across the studies (see Table 5c).[21,22] The use of corticosteroids also varied across the studies.

An extension of the COV-BARRIER trial compared the efficacy of baricitinib to placebo in 101 critically ill patients with COVID-19. The study reported significant reductions in mortality (relative reduction of 46% at 28 days and 44% at 60 days) and no major adverse events among patients who received baricitinib.[23] Systematic reviews of JAK inhibitors confirm the efficacy of using baricitinib in hospitalized patients with COVID-19 who require oxygen support. There is a lower certainty of evidence for patients who were receiving mechanical ventilation or ECMO, and baricitinib may have modestly attenuated efficacy in this group.[24] Baricitinib or tocilizumab should only be administered in combination with dexamethasone or another corticosteroid.

Regarding the use of tofacitinib and sarilumab if baricitinib and tocilizumab are not available or feasible to use, please refer to the rationale for patients who require HFNC oxygen or NIV.

Recommendation

- The Panel recommends using **dexamethasone alone** for the treatment of patients with COVID-19

who require mechanical ventilation or ECMO if baricitinib, tofacitinib, tocilizumab, or sarilumab cannot be obtained **(AI)**.

Dexamethasone was shown to reduce mortality in critically ill patients with COVID-19 in a meta-analysis that aggregated 7 randomized trials and included data on 1,703 critically ill patients. The largest trial in the meta-analysis was the RECOVERY trial, which included a subgroup of patients who were receiving mechanical ventilation (see Corticosteroids and Table 5a).[2] However, as noted above, subsequent studies of immunomodulator therapy suggest that using a combination of dexamethasone and another immunomodulator is more effective in patients with COVID-19 who require mechanical ventilation or ECMO.

Considerations for the Use of Remdesivir

Remdesivir is most effective against COVID-19 in patients who are earlier in the course of the disease and who do not require mechanical ventilation or ECMO. However, in the Solidarity trial, among patients who were receiving mechanical ventilation or ECMO, there was a trend toward an increase in mortality for patients treated with remdesivir.[6] For patients who started on remdesivir and progressed to requiring mechanical ventilation or ECMO, the Panel suggests continuing remdesivir until the treatment course is completed.

Subgroup analyses from 2 randomized trials suggest there is no clinical benefit to using a combination of remdesivir and dexamethasone in patients who are receiving mechanical ventilation or ECMO.[5,15] The data are inconclusive on whether corticosteroid therapy may delay viral clearance in patients with COVID-19.[25-29] Given the conflicting results from observational studies and the lack of clinical trial data, some Panel members would add remdesivir to dexamethasone and a second immunomodulator only in patients who have recently been placed on mechanical ventilation.

Use of Anticoagulants

- The Panel recommends using a **prophylactic dose of heparin** as VTE prophylaxis, unless a contraindication exists **(AI)**; **(BIII)** for pregnant patients.
- For patients who are started on a therapeutic dose of heparin in a non-ICU setting for the management of COVID-19 and then transferred to the ICU, the Panel recommends switching from the therapeutic dose to a **prophylactic dose of heparin**, unless there is another indication for therapeutic anticoagulation **(BIII)**.
- The Panel **recommends against** the use of an **intermediate dose** (e.g., enoxaparin 1 mg/kg daily) and a **therapeutic dose of anticoagulation** for VTE prophylaxis in critically ill patients with COVID-19, except in a clinical trial **(BI)**.

Patients who required mechanical ventilation or ECMO were included in the multiplatform REMAP-CAP/ACTIV-4a/ATTACC and INSPIRATION trials that studied therapeutic doses and intermediate doses of heparin, respectively.[19,20] Because these studies reported no benefits to using intermediate or therapeutic doses of heparin, the recommendations for using prophylactic doses of heparin in hospitalized patients who require mechanical ventilation or ECMO are the same as those for patients who require HFNC oxygen or NIV.

Table 2c. Dosing Regimens for the Drugs Recommended in Table 2b

The drugs in this table are listed in alphabetical order.

Drug Name	Dosing Regimen	Comments
Baricitinib	BAR dose is dependent on eGFR; duration of therapy is up to 14 days or until hospital discharge (whichever comes first).	• eGFR ≥60 mL/min/1.73 m^2: BAR 4 mg PO once daily • eGFR 30 to <60 mL/min/1.73 m^2: BAR 2 mg PO once daily • eGFR 15 to <30 mL/min/1.73 m^2: BAR 1 mg PO once daily • eGFR <15 mL/min/1.73 m^2: BAR **is not recommended**.
Dexamethasone	DEX 6 mg IV or PO once daily for up to 10 days or until hospital discharge (whichever comes first)	• If DEX is not available, an equivalent dose of another corticosteroid may be used. • For more information, see Corticosteroids.
Heparin	Therapeutic dose of SUBQ LMWH or IV UFH	• Administer for 14 days or until hospital discharge (whichever comes first) unless there is a diagnosis of VTE or another indication for therapeutic anticoagulation.
	Prophylactic dose of SUBQ LMWH or SUBQ UFH	• Administer for the duration of the hospital stay.
Remdesivir	RDV 200 mg IV once, then RDV 100 mg IV once daily for 4 days or until hospital discharge (whichever comes first)	• If the patient is hospitalized for reasons other than COVID-19, the treatment duration is 3 days (see Therapeutic Management of Nonhospitalized Adults With COVID-19). • If the patient progresses to more severe illness, complete the course of RDV. • For a discussion on using RDV in patients with renal insufficiency, see Remdesivir.
Sarilumab	Use the single-dose, prefilled syringe (**not** the prefilled pen) for SUBQ injection. Reconstitute sarilumab 400 mg in 100 cc 0.9% NaCl and administer as an IV infusion over 1 hour.	• Use if BAR or tocilizumab is not available or not feasible to use **(BIIa)**. • In the United States, the currently approved route of administration for sarilumab is SUBQ injection. In the REMAP-CAP trial, the SUBQ formulation was used to prepare the IV infusion.
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.
Tofacitinib	Tofacitinib 10 mg PO twice daily for up to 14 days or until hospital discharge (whichever comes first)	• Use if BAR or tocilizumab is not available or not feasible to use **(BIIa)**. • eGFR <60 mL/min/1.73 m^2: tofacitinib 5 mg PO twice daily

Key: BAR = baricitinib; DEX = dexamethasone; eGFR = estimated glomerular filtration rate; IV = intravenous; LMWH = low-molecular-weight heparin; NaCl = sodium chloride; PO = oral; RDV = remdesivir; SUBQ = subcutaneous; UFH = unfractionated heparin; VTE = venous thromboembolism

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Clinical Management of Children Summary

Last Updated: December 28, 2022

Data from the Centers for Disease Control and Prevention demonstrate a lower incidence of SARS-CoV-2 infection, severe disease, and death in children compared with adults.[1-4] Although only a small percentage of children with COVID-19 will require medical attention, the percentage of intensive care unit admissions among hospitalized children is comparable to the percentage among hospitalized adults with COVID-19.[5-16]

Risk factors for severe COVID-19 have been identified through observational studies and meta-analyses primarily conducted before the availability of COVID-19 vaccines. Risk factors include having ≥1 severe comorbid conditions, such as medical complexity with respiratory technology dependence, a neurologic condition resulting in impaired mucociliary clearance, obesity (particularly severe obesity), severe underlying cardiac or pulmonary disease, or severely immunocompromised status. However, pediatric data on risk factors for severe COVID-19 are generally more limited and provide lower certainty than data for adults.

In general, COVID-19 has similar clinical manifestations and disease stages in children and adults, including an early phase driven by viral replication and a late phase that appears to be driven by a dysregulated immune/inflammatory response to SARS-CoV-2 that leads to tissue damage. Respiratory complications in young children that can occur during the early clinical phase include croup and bronchiolitis. In addition, a small number of children who have recovered from acute SARS-CoV-2 infection develop multisystem inflammatory syndrome in children (MIS-C) 2 to 6 weeks after infection. MIS-C is a postinfectious inflammatory condition that can lead to severe organ dysfunction, which is in contrast to COVID-19, the acute, primarily respiratory illness due to infection with SARS-CoV-2.

There are no results available from clinical trials that evaluated treatments for COVID-19 in children, and data from observational studies are limited. Applying adult data from COVID-19 trials to children is a unique challenge because most children experience a mild course of illness with COVID-19. Relative to adults, children with COVID-19 have substantially lower mortality and less need for hospitalization. Because of these differences in epidemiology and disease severity, the effect sizes for children are likely to be smaller than those observed in adults; therefore, to produce a beneficial outcome, the number needed to treat is higher. Collectively, these factors influence the risk versus benefit balance for pharmacologic therapies in children.

In the absence of sufficient clinical trial data on the treatment of children with COVID-19, the COVID-19 Treatment Guidelines Panel's (the Panel) recommendations for the therapeutic management of children are based largely on adult safety and efficacy data from clinical trials, the child's risk of disease progression, and expert opinion. In general, the older the child and the more severe the disease, the more reasonable it is to follow treatment recommendations for adult patients with COVID-19.

The Panel's recommendations for the management of children with COVID-19 or MIS-C are summarized in the tables below. Table 3a provides recommendations for the therapeutic management of nonhospitalized children with COVID-19. The Panel's recommendations are stratified by age (per the Food and Drug Administration Emergency Use Authorizations) and risk level. See Therapeutic Management of Nonhospitalized Children With COVID-19 for more information. Table 3b includes a framework to help clinicians evaluate the risk for severe COVID-19 based on patient conditions and COVID-19 vaccination status.

The recommendations for hospitalized children in Table 3c are stratified by disease severity. See Therapeutic Management of Hospitalized Children With COVID-19 for more information. Table 3d summarizes the recommendations for the therapeutic management of MIS-C. For the rationale behind these recommendations and supporting data, see Therapeutic Management of Hospitalized Pediatric Patients With Multisystem Inflammatory Syndrome in Children (MIS-C) (With Discussion on Multisystem Inflammatory Syndrome in Adults [MIS-A]).

Table 3a. Therapeutic Management of Nonhospitalized Children With COVID-19

Risk of Severe COVID-19	Panel's Recommendations	
	Aged 12–17 years	Aged <12 years
Symptomatic, Regardless of Risk Factors	• Provide supportive care **(AIII)**.	• Provide supportive care **(AIII)**.

High Risk[a,b]	• Use 1 of the following options (listed in order of preference):[c]
	  • **Ritonavir-boosted nirmatrelvir (Paxlovid)** within 5 days of symptom onset **(BIII)**
	  • **Remdesivir** within 7 days of symptom onset **(CIII)**
		• Ritonavir-boosted nirmatrelvir is not authorized by the FDA for use in children aged <12 years.
		• There is insufficient evidence to recommend either for or against routine use of remdesivir. Consider treatment based on age and other risk factors.

Intermediate Risk[b,d]	• There is insufficient evidence to recommend either for or against the use of any antiviral therapy. Consider treatment based on age and other risk factors.	• There is insufficient evidence to recommend either for or against routine use of remdesivir.
Low Risk[b,e]	• Manage with supportive care alone **(BIII)**.	• Manage with supportive care alone **(BIII)**.
Each recommendation in the Guidelines receives 2 ratings that reflect the strength of the recommendation and the quality of the evidence that supports it. See Guidelines Development for more information.		

[a] Molnupiravir is not authorized by the FDA for use in children aged <18 years and should not be used.

[b] See Table 3b for the Panel's framework for assessing the risk of progression to severe COVID-19 based on patient conditions and COVID-19 vaccination status.

[c] Initiate treatment as soon as possible after symptom onset.

[d] The relative risk of severe COVID-19 for intermediate-risk patients is lower than the risk for high-risk patients but higher than the risk for low-risk patients.

[e] Low-risk patients include those with comorbid conditions that have a weak or unknown association with severe COVID-19. Patients with no comorbidities are included in this group.

Key: FDA = Food and Drug Administration; the Panel = the COVID-19 Treatment Guidelines Panel

Table 3b. The Panel's Framework for Assessing the Risk of Progression to Severe COVID-19 Based on Patient Conditions and COVID-19 Vaccination Status

Conditions	Risk Level by Vaccination Status[a]		
	Unvaccinated	Primary Series	Up to Date
Strong or Consistent Association With Progression to Severe COVID-19			
• Moderately or severely immunocompromised (see Special Considerations in People Who Are Immunocompromised)	High		
• Obesity (BMI ≥95th percentile for age), especially severe obesity (BMI ≥120% of 95th percentile for age)[b] • Medical complexity with dependence on respiratory technology[c] • Severe neurologic, genetic, metabolic, or other disability that results in impaired airway clearance or limitations in self care or activities of daily living • Severe asthma or other severe chronic lung disease requiring ≥2 inhaled or ≥1 systemic medications daily • Severe congenital or acquired cardiac disease • Multiple moderate to severe chronic diseases	High	Intermediate	
Moderate or Inconsistent Association With Progression to Severe COVID-19			
• Aged <1 year • Prematurity in children aged ≤2 years • Sickle cell disease • Diabetes mellitus (poorly controlled) • Nonsevere cardiac, neurologic, or metabolic disease[d]	Intermediate		
Weak or Unknown Association With Progression to Severe COVID-19			
• Mild asthma • Overweight • Diabetes mellitus (well controlled)	Low		

[a] **Unvaccinated** = individuals who are not eligible for COVID-19 vaccination or are <2 weeks from the final dose of the primary series. **Vaccinated with primary series** = individuals who completed the primary series of 2 or 3 doses (the current CDC term is "fully vaccinated") and are >2 weeks after the final dose of the primary series but have not received a booster, if they are eligible for a booster. Children aged <5 years are not currently eligible for booster doses. **Vaccinated and up to date** = individuals who received the recommended booster dose(s) if eligible or have completed the primary series but are not yet eligible for a booster. See the COVID-19 vaccination schedule from the CDC for more information.

[b] The degree of risk conferred by obesity in younger children is less clear than it is in older adolescents.

[c] This includes patients with a tracheostomy and those who require NIV.

[d] The data for this group are particularly limited.

Key: BMI = body mass index; CDC = Centers for Disease Control and Prevention; NIV = noninvasive ventilation; the Panel = the COVID-19 Treatment Guidelines Panel

Table 3c. Therapeutic Management of Hospitalized Children With COVID-19

Disease Severity	Panel's Recommendations
Hospitalized for COVID-19	For children aged ≥12 years admitted for COVID-19, use prophylactic anticoagulation unless contraindicated **(BIII)**.
Does Not Require Supplemental Oxygen	For children admitted for COVID-19 who are at the highest risk of progression to severe COVID-19,[a] consider using **remdesivir**[b] for children aged 12–17 years **(CIII)**. There is insufficient evidence for using remdesivir in children aged 28 days to <12 years.
	For children admitted for reasons other than COVID-19 who have mild to moderate COVID-19 and are at the highest risk of progression,[a] refer to Therapeutic Management of Nonhospitalized Children With COVID-19.
Requires Conventional Oxygen[c]	Use 1 of the following options: • **Remdesivir**[b] **(BIII)** • **Dexamethasone plus remdesivir**[b] for children with increasing oxygen needs, particularly adolescents **(BIII)**
Requires Oxygen Through High-Flow Device or NIV[d]	Use 1 of the following options: • **Dexamethasone (BIII)** • **Dexamethasone plus remdesivir**[b] **(BIII)**
	For children who do not have rapid (e.g., within 24 hours) improvement in oxygenation after initiation of dexamethasone, **baricitinib**[e] or **tocilizumab** can be considered for children aged 12–17 years **(BIII)** and for children aged 2–11 years **(CIII)**.
Requires MV or ECMO[f]	**Dexamethasone**[f] **(AIII)**
	For children who do not have rapid (e.g., within 24 hours) improvement in oxygenation after initiation of dexamethasone, **baricitinib**[e] or **tocilizumab** may be considered for children aged 12–17 years **(BIII)** and for children aged 2–11 years **(CIII)**.
Each recommendation in the Guidelines receives 2 ratings that reflect the strength of the recommendation and the quality of the evidence that supports it. See Guidelines Development for more information.	

[a] For example, for children who are severely immunocompromised regardless of COVID-19 vaccination status and those who are unvaccinated and have additional risk factors for progression (see Therapeutic Management of Nonhospitalized Children With COVID-19).

[b] The clinical benefit of remdesivir is greatest if it is initiated within 10 days of symptom onset. Remdesivir should be given for 5 days or until hospital discharge, whichever comes first.

[c] Conventional oxygen refers to oxygen supplementation that is not high-flow oxygen, NIV, MV, or ECMO.

[d] Patients who are receiving NIV or MV at baseline and require a substantial increase in baseline support should be treated per the recommendations for patients requiring new NIV or MV.

[e] **Tofacitinib** is an alternative if baricitinib is not available **(BIII)**.

[f] For children who started receiving remdesivir before admission to the ICU, the remdesivir should be continued to complete the treatment course.

Key: ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; MV = mechanical ventilation; NIV = noninvasive ventilation

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

Patient Condition	Panel's Recommendations

MIS-C	**Initial treatment for MIS-C includes both immunomodulatory and antithrombotic therapy.**
	Initial Immunomodulatory Therapy
	• **IVIG** 2 g/kg IBW/dose (up to a maximum total dose of 100 g)[a] IV **plus** low-to-moderate dose **methylprednisolone** (1–2 mg/kg/day) IV[a] or another glucocorticoid at an equivalent dosea **(AIIb)**.
	• The Panel recommends against the routine use of IVIG monotherapy for the treatment of MIS-C unless glucocorticoid use is contraindicated **(AIIb)**.
	Intensification Immunomodulatory Therapy
	• For children with refractory MIS-C who do not improve within 24 hours of initial immunomodulatory therapy, start 1 of the following (listed in alphabetical order) **(AIII)**:
	  • High-dose **anakinra** 5–10 mg/kg IV or SUBQ daily **(BIIb)**, *or*
	  • **Higher-dose glucocorticoid** (e.g., **methylprednisolone** 10–30 mg/kg/day IV or equivalent glucocorticoid) **(BIIb)**,[b] *or*
	  • **Infliximab**[c] 5–10 mg/kg IV for 1 dose **(BIIb)**.
	Antithrombotic Treatment
	• Low-dose **aspirin** (3–5 mg/kg/day, up to maximum daily dose of 81 mg) PO for all patients without risk factors for bleeding **(AIII)**, **AND**
	• Anticoagulation for patients who fall under 1 of the following clinical scenarios:
	  • **Therapeutic anticoagulation** for patients with large CAAs according to the American Heart Association guidelines for Kawasaki disease **(AIII)**.
	  • **Therapeutic anticoagulation** for patients with moderate to severe LV dysfunction who have no risk factors for bleeding **(AIII)**.
	  • For patients with MIS-C who do not have large CAAs or moderate to severe LV dysfunction, consider **prophylactic or therapeutic anticoagulation** on an individual basis, taking into consideration risk factors for thrombosis. See Table 3e for additional information.

Each recommendation in the Guidelines receives 2 ratings that reflect the strength of the recommendation and the quality of the evidence that supports it. See Guidelines Development for more information.	

[a] Duration of therapy may vary. For more information, see Therapeutic Management of Hospitalized Pediatric Patients With Multisystem Inflammatory Syndrome in Children (MIS-C) (With Discussion on Multisystem Inflammatory Syndrome in Adults [MIS-A]).

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

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

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

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Special Considerations in Children

Last Updated: August 8, 2022

Key Considerations
• SARS-CoV-2 infection is generally milder in children than in adults, and a substantial proportion of children with the infection are asymptomatic. • Most nonhospitalized children with COVID-19 will not require any specific therapy. • Observational studies describe associations between severe COVID-19 and the presence of ≥1 comorbid conditions, including cardiac disease, neurologic disorders, prematurity (in young infants), diabetes, obesity (particularly severe obesity), chronic lung disease, feeding tube dependence, and immunocompromised status. Age (<1 year and 10–14 years) and non-White race/ethnicity are also associated with severe disease. • Most children hospitalized for severe COVID-19 have not been fully vaccinated or are not eligible for COVID-19 vaccination. • Data on the pathogenesis and clinical spectrum of SARS-CoV-2 infection are more limited for children than for adults. • Vertical transmission of SARS-CoV-2 appears to be rare, but suspected or probable cases of vertical transmission have been described. • A small subset of children and young adults with SARS-CoV-2 infection may develop multisystem inflammatory syndrome in children (MIS-C). Many patients with MIS-C require intensive care management. The majority of children with MIS-C do not have underlying comorbid conditions. • Data on the prevalence of post-COVID conditions in children are limited but suggest that younger children may have fewer persistent symptoms than older children and adults.
Each recommendation in the Guidelines receives 2 ratings that reflect the strength of the recommendation and the quality of the evidence that supports it. See Guidelines Development for more information.

This section provides an overview of the epidemiology and clinical spectrum of disease, including COVID-19, multisystem inflammatory syndrome in children (MIS-C), and post-COVID conditions. This section also includes information on risk factors for severe COVID-19, vertical transmission, and infants born to a birth parent with SARS-CoV-2 infection. Throughout this section, COVID-19 refers to the acute, primarily respiratory illness due to infection with SARS-CoV-2. MIS-C refers to the postinfectious inflammatory condition.

For information on the prevention, treatment, and management of severe complications of COVID-19 in children, see:

- Prevention of SARS-CoV-2 Infection
- Therapeutic Management of Hospitalized Children With COVID-19
- Therapeutic Management of Hospitalized Pediatric Patients With Multisystem Inflammatory Syndrome in Children (MIS-C) (With Discussion on Multisystem Inflammatory Syndrome in Adults [MIS-A])
- Introduction to Critical Care Management of Children With COVID-19

Epidemiology

Data from the Centers for Disease Control and Prevention (CDC) demonstrate that SARS-CoV-2 infection and severe disease and death due to COVID-19 occur less often in children than in adults.[1-4] However, the true burden of pediatric SARS-CoV-2 infection remains unclear, as children with mild

symptoms are seldom systematically tested, and contact tracing and seroprevalence studies are not generally conducted. Seroprevalence data have suggested that, as of mid-2021, most children did not have evidence of prior SARS-CoV-2 infection. However, among children and adolescents, the estimated number of SARS-CoV-2 infections that occurred through May 2021 was 4.7 to 8.9 times greater than the number of COVID-19 cases.[5] In a report from the CDC, by February 2022, approximately 75% of children and adolescents had serologic evidence of prior SARS-CoV-2 infection.[6]

Data on the pathogenesis and disease severity of SARS-CoV-2 infection in children are increasing but are still limited compared to the adult data. Although only a small percentage of children with COVID-19 will require medical attention, the percentage of intensive care unit (ICU) admissions among hospitalized children is comparable to that for hospitalized adults with COVID-19.[7-18]

Children from some racial and ethnic groups experience disproportionate rates of COVID-19-related hospitalization, which may be a result of barriers to accessing health care and economic and structural inequities. From 2020 to 2021, Black/African American children with COVID-19 in the United States were 2 times more likely to be hospitalized and 5 times more likely to be admitted to the ICU than White children.[19]

A U.S. study of children with COVID-19 who were hospitalized between April and September 2020 reported an association between race/ethnicity and disease severity.[20] In a large United Kingdom study, admission to critical care was independently associated with hospitalized children who self-reported as being of Black ethnicity.[14] A study in England reported that children who identified as Asian were more likely than children who identified as White to be hospitalized for COVID-19 and to be admitted to an ICU.[21] The study also found that children who identified as Black or as mixed or other races/ethnicities had significantly more hospitalizations than children who identified as White.

Clinical Manifestations of COVID-19

The signs and symptoms of SARS-CoV-2 infection in symptomatic children may be similar to those in adults; however, a greater proportion of children may be asymptomatic or have only mild illness when compared with adults. Although the true incidence of asymptomatic SARS-CoV-2 infection is unknown, a small study reported that 45% of children who underwent surveillance testing at the time of hospitalization for a non-COVID-19 indication had asymptomatic infection.[22] The most common signs and symptoms of COVID-19 in hospitalized children are fever, nausea/vomiting, cough, shortness of breath, and upper respiratory symptoms.[14,23] The signs and symptoms of COVID-19 may overlap significantly with those of influenza and other respiratory and enteric viral infections. Critical disease, including respiratory failure, acute respiratory distress syndrome, and, less commonly, shock, may occur in children with COVID-19.[24,25] The overall incidence of SARS-CoV-2 infection and, by extension, COVID-19-related hospitalizations among children has increased substantially with the emergence of recent variants of concern (VOCs), particularly Omicron.[18,26]

Risk Factors for Severe COVID-19

Risk factors for severe COVID-19 identified by observational studies and meta-analyses include having ≥1 comorbidities, such as cardiac disease, neurologic disorders, prematurity (in young infants), diabetes, obesity (particularly severe obesity), chronic lung disease, feeding tube dependence, and immunocompromised status. Demographic factors, such as age (<1 year and 10–14 years) and non-White race/ethnicity, have also been associated with severe disease. However, many studies did not assess the relative severity of underlying medical conditions.

Many published studies reported an increased relative risk of severe disease in children with comorbidities, but the absolute risk of severe COVID-19 among children remains low. However,

protocolized admissions for certain populations (e.g., febrile young infants) may confound the association between comorbid conditions and severe COVID-19. Most children who have been hospitalized for severe COVID-19 have not been fully vaccinated—many were not eligible for COVID-19 vaccination because of their age. The CDC has additional information on the underlying conditions that are risk factors for severe COVID-19.

The children most likely to benefit from treatment are nonhospitalized patients with mild to moderate COVID-19 who are at the highest risk for severe COVID-19 (e.g., those with severe comorbidities). For a description of children considered at high risk for severe COVID-19 and the COVID-19 Treatment Guidelines Panel's (the Panel) recommendations for their treatment, see Therapeutic Management of Hospitalized Children With COVID-19.

Age

Among all children, infants and adolescents have the highest risk of COVID-19-related ICU admission or death. From March 2020 to mid-August 2021, U.S. children aged <5 years had the highest cumulative COVID-19-related hospitalization rates, followed closely by adolescents.[27] Children aged 5 to 11 years had the lowest hospitalization rates. From July to August 2021, when the Delta variant was the dominant VOC, 25% of 713 children admitted to 6 U.S. hospitals were aged <1 year, 17% were aged 1 to 4 years, 20% were aged 5 to 11 years, and 38% were aged 12 to 17 years.[28] From March 2020 to mid-June 2021, 26.5% of 3,116 U.S. children hospitalized for COVID-19 were admitted to an ICU.[27]

An individual patient data meta-analysis reported that patients aged <1 year and those aged 10 to 14 years had the highest risks of ICU admission and death among hospitalized children with COVID-19.[29] Another meta-analysis reported that neonates, but not infants aged 1 to 3 months, had an increased risk of severe COVID-19 compared with other pediatric age groups.[30] When Omicron was the dominant circulating VOC, hospitalization rates among children and adolescents were higher than when the Delta VOC was dominant, and they were highest for children aged <5 years.[26,31] However, the proportion of hospitalized children requiring ICU admission was significantly lower when the Omicron VOC was dominant.

Comorbidities

Several chronic conditions are prevalent in hospitalized children with COVID-19. When the Delta variant was the dominant VOC in the United States, 68% of hospitalized children had ≥1 underlying medical condition, such as obesity (32%), asthma or reactive airway disease (16%), or feeding tube dependence (8%). Obesity was present in approximately a third of hospitalized children aged 5 to 11 years, 60% of whom had a body mass index (BMI) ≥120% of the 95th percentile. For adolescents, 61% had obesity; of those patients, 61% had a BMI ≥120% of the 95th percentile.[28]

Meta-analyses and observational studies identified risk factors for ICU admission, mechanical ventilation, or death among hospitalized children with COVID-19.[30,32,33] These risk factors included prematurity in young infants, obesity, diabetes, chronic lung disease, cardiac disease, neurologic disease, and immunocompromising conditions. Another study found that having a complex chronic condition that affected ≥2 body systems or having a progressive chronic condition or continuous dependence on technology for ≥6 months (e.g., dialysis, tracheostomy with ventilator assistance) was significantly associated with an increased risk of moderate or severe COVID-19.[34] The study also found that having more severe chronic disease (e.g., active cancer treated within the previous 3 months or asthma with hospitalization within the previous 12 months), when compared with less severe conditions, increased the risk of critical COVID-19 or death. The CDC has additional information on the underlying conditions that are risk factors for severe COVID-19.

Having multiple comorbidities increases the risk of severe COVID-19 in children. A meta-analysis of data from children hospitalized with COVID-19 found that the risk of ICU admission was greater for children with 1 chronic condition than for those with no comorbid conditions, and the risk increased substantially as the number of comorbidities increased.[29]

COVID-19 Vaccination Status

Vaccination remains the most effective way to prevent SARS-CoV-2 infection and should be considered the first line of prevention. Most children hospitalized for COVID-19 were not fully vaccinated or were not eligible to receive COVID-19 vaccination because of their age.[16,18,28,35] With the wider availability of COVID-19 vaccines for younger children, the number of COVID-19 cases among children may decrease over time.

Mortality

Death from COVID-19 is uncommon in children. Risk factors for death include having chronic conditions, such as neurologic or cardiac disease, and having multiple comorbidities. Among children aged <21 years in the United States, deaths associated with COVID-19 have been higher for children aged 10 to 20 years, especially for young adults aged 18 to 20 years, and for those who identify as Hispanic, Black, or American Indian/Alaskan Native.[36,37]

A systematic review and meta-analysis reported that neurologic or cardiac comorbidities were associated with the greatest increase in risk of death among hospitalized children with COVID-19.[29] In the same study, an individual patient data meta-analysis reported that the risk of COVID-19-related death was greater for children with 1 chronic condition than for those with no comorbid conditions, and the risk increased substantially as the number of comorbidities increased.

Vertical Transmission and Infants Born to People With SARS-CoV-2 Infection

A systematic review and meta-analysis reported that confirmed vertical transmission of SARS-CoV-2 appears to be rare, and severe maternal COVID-19 has been associated with SARS-CoV-2 infection in babies.[38] In 2 large, combined cohorts of pregnant individuals from the United States and United Kingdom, SARS-CoV-2 infection was reported in 1.8% and 2% of the babies born to people with SARS-CoV-2 infection.[39]

Case reports have described intrauterine fetal demise during the third trimester of pregnancy in individuals with mild COVID-19 due to infection with the Delta VOC.[40,41] These individuals had evidence of placental SARS-CoV-2 infection, placental malperfusion, and placental inflammation. One case report described a person with asymptomatic SARS-CoV-2 infection and severe preeclampsia who gave birth at 25 weeks of gestation by emergency cesarean delivery. The neonate died on Day 4, and evidence of SARS-CoV-2 infection was found in placental tissues and in the infant's lungs and vascular endothelium at autopsy.[42] Evidence of placental SARS-CoV-2 infection was reported in 5 stillbirths and for 1 live-born neonate in Sweden.[43]

A systematic review of neonatal SARS-CoV-2 infections reported that 70% were due to postpartum transmission, and 30% were due to vertical transmission from an infected birth parent.[44] Another systematic review reported that newborn infants rooming-in with the birth parent did not have an increased risk of SARS-CoV-2 transmission when compared with newborns who were isolated from the birth parent.[45]

Detection of SARS-CoV-2 RNA in the breast milk of individuals with confirmed cases of COVID-19 is very uncommon.[46] Currently, there is no evidence of SARS-CoV-2 transmission through breast milk.[47]

Breast milk from people with SARS-CoV-2 infection can contain antibodies to SARS-CoV-2.[48,49]

Multisystem Inflammatory Syndrome in Children

A small subset of children and young adults with SARS-CoV-2 infection, including those with asymptomatic infection, may develop MIS-C. This syndrome is also called pediatric multisystem inflammatory syndrome—temporally associated with SARS-CoV-2 (PMIS-TS). Although the case definitions for these syndromes differ slightly, they are likely the same disease. The syndrome was first described in Europe, where previously healthy children with severe inflammation and Kawasaki disease-like features were identified as having current or recent infection with SARS-CoV-2.

The clinical spectrum of MIS-C has been described in the United States and is similar to that described for PMIS-TS. MIS-C is consistent with a postinfectious inflammatory syndrome related to SARS-CoV-2.[50,51] Most patients with MIS-C have serologic evidence of previous SARS-CoV-2 infection, but only a minority have had a positive reverse transcription polymerase chain reaction (RT-PCR) result for SARS-CoV-2 at presentation.[52,53]

The peak population-based incidence of MIS-C lags about 4 weeks behind the peak of acute pediatric COVID-19-related hospitalizations. Emerging data suggests that adults may develop a similar syndrome, multisystem inflammatory syndrome in adults (MIS-A), although it is not clear if this postinfectious complication is similar to MIS-C.[52-54] Published data that characterize the condition are limited.

Although risk factors for the development of MIS-C have not been established, an analysis of MIS-C cases in the United States found that ICU admission was more likely for patients aged 6 to 12 years than for younger children, and it was more likely for children who identified as non-Hispanic Black than for those who identified as non-Hispanic White.[55] Unlike most children who present with severe COVID-19, the majority of children who present with MIS-C do not seem to have common underlying comorbid conditions other than obesity.[55] In addition, children whose deaths were related to MIS-C were less likely to have underlying medical conditions than children who died of COVID-19.[37]

Emerging evidence suggests that COVID-19 vaccination protects against the development of MIS-C.[56,57] The development of MIS-C after COVID-19 vaccination is very rare.[56,58]

Clinical Manifestations of Multisystem Inflammatory Syndrome in Children

The current CDC case definition for MIS-C is an individual aged <21 years who:

- Presents with fever,[a] laboratory evidence of inflammation,[b] and evidence of clinically severe illness requiring hospitalization, with multisystem (i.e., >2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological); *and*
- Has no alternative plausible diagnoses; *and*
- Is positive for current or recent SARS-CoV-2 infection by RT-PCR, antigen test, or serology results; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms.[59]

[a] Fever >38.0°C for ≥24 hours or report of subjective fever lasting ≥24 hours

[b] Including, but not limited to, ≥1 of the following: elevated levels of C-reactive protein, fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase, or interleukin (IL)-6; an elevated erythrocyte sedimentation rate or neutrophil count; or a reduced lymphocyte count or albumin level

Distinguishing MIS-C from other febrile illnesses in the community setting remains challenging, but the presence of persistent fever, multisystem manifestations, and laboratory abnormalities could help early recognition.[60] The clinical spectrum of hospitalized cases has included younger children with mucocutaneous manifestations that overlap with Kawasaki disease, older children with more multiorgan

involvement and shock, and patients with respiratory manifestations that overlap with COVID-19.

Patients with MIS-C are often critically ill, and up to 80% of children require ICU admission.[61] Most patients with MIS-C have markers of cardiac injury or dysfunction, including elevated levels of troponin and brain natriuretic protein; higher levels of these markers are associated with ICU admission, myocardial dysfunction, and shock.[55] In these cases, echocardiographic findings may include impaired left ventricular function, coronary artery dilations, and, rarely, coronary artery aneurysms. The reported mortality in the United States for hospitalized children with MIS-C is 1% to 2%. Longitudinal studies to examine the long-term sequelae of MIS-C are currently ongoing.

The pathogenesis of MIS-C is still being elucidated and may include distinct humoral immune responses, innate immune activation, or a superantigen effect. Differences between MIS-C and typical Kawasaki disease have been demonstrated 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 COVID-19 in children.[62-64]

For the Panel's recommendations on the treatment of MIS-C, see Therapeutic Management of Hospitalized Pediatric Patients With Multisystem Inflammatory Syndrome in Children (MIS-C) (With Discussion on Multisystem Inflammatory Syndrome in Adults [MIS-A]).

Post-COVID Conditions

Persistent symptoms after COVID-19 have been described in adults and are an active area of research in children, although data on the incidence of post-COVID sequelae in children are limited and somewhat conflicting (see Clinical Spectrum of SARS-CoV-2 Infection).[65-67] Cardiac imaging studies have described myocardial injury in young athletes who had only mild disease;[68] additional studies are needed to identify long-term cardiac sequelae.

The reported clinical manifestations and duration of post-COVID conditions in children are highly variable.[69] Not all studies included controls without SARS-CoV-2 infection, which makes determining the true incidence a challenge. The incidence of post-COVID symptoms appears to increase with age. The most common symptoms reported include persistent fatigue, headache, shortness of breath, sleep disturbances, and altered sense of smell.

Among children, health care utilization increases following COVID-19. A Norwegian study of 10,279 children with and 275,859 without SARS-CoV-2 infection reported that primary care visits for children aged 6 to 15 years increased for up to 3 months after a positive SARS-CoV-2 test result when compared with controls.[66,70] For preschool-age children, visits increased for up to 6 months.

In a study of 6,804 adolescents in England, 30% of the 3,065 participants who tested positive for SARS-CoV-2 infection reported ≥3 symptoms at a 3-month follow-up visit.[71] Common symptoms included tiredness (39%), headache (23%), and shortness of breath (23%). In the same study, only 16% of the 3,739 participants who tested negative for SARS-CoV-2 infection reported ≥3 symptoms at the 3-month follow-up visit.

A study in Denmark examined persistent symptoms among 16,836 children with and 16,620 children without SARS-CoV-2 infection. The number of children with SARS-CoV-2 infection who reported symptoms that persisted for >4 weeks increased as age increased. Among the preschool-age children, more children in the control arm than in the SARS-CoV-2 arm reported experiencing symptoms that persisted for >4 weeks.[72]

Additional research is needed to define the incidence, spectrum, and severity of post-COVID conditions

in children and to identify optimal strategies for prevention, diagnosis, and treatment of those conditions.

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Therapeutic Management of Nonhospitalized Children With COVID-19

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This section outlines the COVID-19 Treatment Guidelines Panel's (the Panel) recommendations for the therapeutic management of nonhospitalized children (i.e., pediatric patients aged <18 years) with mild to moderate COVID-19. These recommendations are also for children who have mild to moderate COVID-19 and are hospitalized for reasons other than COVID-19. For patients aged ≥18 years, see Therapeutic Management of Nonhospitalized Adults With COVID-19. Throughout this section, the term "COVID-19" refers to the acute, primarily respiratory illness caused by infection with SARS-CoV-2. For the Panel's recommendations for managing multisystem inflammatory syndrome in children (MIS-C), see Therapeutic Management of Hospitalized Pediatric Patients With Multisystem Inflammatory Syndrome in Children (MIS-C) (With Discussion on Multisystem Inflammatory Syndrome in Adults [MIS-A]).

Treatment Considerations for Children With COVID-19

Currently, no results from pediatric clinical trials that evaluated the treatment of COVID-19 have been published. Data evaluating the use of pharmacologic therapy in children with COVID-19 are limited largely to descriptive reports.[1,2] Therefore, more high-quality randomized trials, observational studies, and pharmacokinetic studies are urgently needed. Whenever possible, clinical trials of therapeutics and multicenter observational cohorts should enroll children with COVID-19.

The current recommendations for treating COVID-19 in children have been mostly extrapolated from recommendations for adults with COVID-19, recommendations for children with other viral infections, and expert opinion.[3-5] Applying adult data from COVID-19 trials to children is a unique challenge, because most children experience a mild course of illness with COVID-19. Relative to adults, children with COVID-19 have substantially lower mortality and less need for hospitalization. Because of these differences in epidemiology and disease severity, the effect sizes for children are likely to be smaller than those observed in adults; therefore, to produce a beneficial outcome, the number needed to treat is higher. Collectively, these factors influence the risk versus benefit balance for pharmacologic therapies in children.

Other challenges are the uncertainty about which comorbid conditions place children at the highest risk of severe COVID-19 and the uncertainty about the absolute magnitude of the increased risk from those comorbid conditions. Clinicians need to consider the number and severity of a child's comorbid conditions when making decisions about pharmacologic treatments for COVID-19. For more information on risk factors for children with COVID-19, see Special Considerations in Children.

Recommendations

In the absence of sufficient clinical trial data on the treatment of children with COVID-19, the Panel's recommendations for the therapeutic management of nonhospitalized children are based largely on adult safety and efficacy data from clinical trials (see Table 3a). No pediatric comparative studies have been published; therefore, all the quality of evidence ratings for the Panel's recommendations in this section are based on expert opinion (i.e., a **III** rating).

The majority of children with mild to moderate COVID-19 will not progress to more severe illness;

therefore, the Panel recommends managing these patients with supportive care alone **(AIII)**. The risks and benefits of therapy should be assessed based on COVID-19 disease severity, age, vaccination status, and the presence of underlying medical conditions that may place the patient at high risk of severe COVID-19.

Table 3a. Therapeutic Management of Nonhospitalized Children With COVID-19

Risk of Severe COVID-19	Panel's Recommendations	
	Aged 12–17 years	Aged <12 years
Symptomatic, Regardless of Risk Factors	• Provide supportive care **(AIII)**.	• Provide supportive care **(AIII)**.

High Risk[a,b]	• Use 1 of the following options (listed in order of preference):[c]
	  • **Ritonavir-boosted nirmatrelvir (Paxlovid)** within 5 days of symptom onset **(BIII)**
	  • **Remdesivir** within 7 days of symptom onset **(CIII)**
		• Ritonavir-boosted nirmatrelvir is not authorized by the FDA for use in children aged <12 years.
		• There is insufficient evidence to recommend either for or against routine use of remdesivir. Consider treatment based on age and other risk factors.

Intermediate Risk[b,d]	• There is insufficient evidence to recommend either for or against the use of any antiviral therapy. Consider treatment based on age and other risk factors.	• There is insufficient evidence to recommend either for or against routine use of remdesivir.
Low Risk[b,e]	• Manage with supportive care alone **(BIII)**.	• Manage with supportive care alone **(BIII)**.
Each recommendation in the Guidelines receives 2 ratings that reflect the strength of the recommendation and the quality of the evidence that supports it. See Guidelines Development for more information.		

[a] Molnupiravir is not authorized by the FDA for use in children aged <18 years and should not be used.

[b] See Table 3b for the Panel's framework for assessing the risk of progression to severe COVID-19 based on patient conditions and COVID-19 vaccination status.

[c] Initiate treatment as soon as possible after symptom onset.

[d] The relative risk of severe COVID-19 for intermediate-risk patients is lower than the risk for high-risk patients but higher than the risk for low-risk patients.

[e] Low-risk patients include those with comorbid conditions that have a weak or unknown association with severe COVID-19. Patients with no comorbidities are included in this group.

Key: FDA = Food and Drug Administration; the Panel = the COVID-19 Treatment Guidelines Panel

Table 3b. The Panel's Framework for Assessing the Risk of Progression to Severe COVID-19 Based on Patient Conditions and COVID-19 Vaccination Status

<table>
<tr><th rowspan="2">Conditions</th><th colspan="3">Risk Level by Vaccination Status[a]</th></tr>
<tr><th>Unvaccinated</th><th>Primary Series</th><th>Up to Date</th></tr>
<tr><td colspan="4">Strong or Consistent Association With Progression to Severe COVID-19</td></tr>
<tr><td>• Moderately or severely immunocompromised (see Special Considerations in People Who Are Immunocompromised)</td><td colspan="3">High</td></tr>
<tr><td>• Obesity (BMI ≥95th percentile for age), especially severe obesity (BMI ≥120% of 95th percentile for age)[b]
• Medical complexity with dependence on respiratory technology[c]
• Severe neurologic, genetic, metabolic, or other disability that results in impaired airway clearance or limitations in self care or activities of daily living
• Severe asthma or other severe chronic lung disease requiring ≥2 inhaled or ≥1 systemic medications daily
• Severe congenital or acquired cardiac disease
• Multiple moderate to severe chronic diseases</td><td>High</td><td colspan="2">Intermediate</td></tr>
<tr><td colspan="4">Moderate or Inconsistent Association With Progression to Severe COVID-19</td></tr>
<tr><td>• Aged <1 year
• Prematurity in children aged ≤2 years
• Sickle cell disease
• Diabetes mellitus (poorly controlled)
• Nonsevere cardiac, neurologic, or metabolic disease[d]</td><td colspan="3">Intermediate</td></tr>
<tr><td colspan="4">Weak or Unknown Association With Progression to Severe COVID-19</td></tr>
<tr><td>• Mild asthma
• Overweight
• Diabetes mellitus (well controlled)</td><td colspan="3">Low</td></tr>
</table>

[a] **Unvaccinated** = individuals who are not eligible for COVID-19 vaccination or are <2 weeks from the final dose of the primary series. **Vaccinated with primary series** = individuals who completed the primary series of 2 or 3 doses (the current CDC term is "fully vaccinated") and are >2 weeks after the final dose of the primary series but have not received a booster, if they are eligible for a booster. Children aged <5 years are not currently eligible for booster doses. **Vaccinated and up to date** = individuals who received the recommended booster dose(s) if eligible or have completed the primary series but are not yet eligible for a booster. See the current COVID-19 vaccination schedule from the CDC for more information.

[b] The degree of risk conferred by obesity in younger children is less clear than it is in older adolescents.

[c] This includes patients with a tracheostomy and those who require NIV.

[d] The data for this group are particularly limited.

Key: BMI = body mass index; CDC = Centers for Disease Control and Prevention; NIV = noninvasive ventilation; the Panel = the COVID-19 Treatment Guidelines Panel

Rationale for the Panel's Framework for Assessing the Risk of Progression to Severe COVID-19

Although mortality associated with COVID-19 in children is low overall, severe disease can occur, especially in those with risk factors.[6] Risk stratification for severe disease in children remains challenging. Imprecise definitions of comorbid conditions, insufficient granularity for differentiating the severity of comorbidities (e.g., mild vs. severe lung disease, poorly controlled vs. well-controlled diabetes), and small sample sizes limit the conclusions that can be drawn from individual studies and make comparing findings across studies difficult.

Furthermore, asymptomatic SARS-CoV-2 infection detected during admission screening for children who are hospitalized for reasons other than COVID-19 may affect the estimated risk of severe COVID-19, particularly for patient groups that may have protocolized admissions (e.g., children with febrile neutropenia, infants aged <90 days with fever). In addition, the published studies that have evaluated these associations in children are limited largely to case series without control groups and observational studies with methodologic limitations.

Despite these challenges, a risk-stratification framework needs to be developed that will allow clinicians to identify the patients who are most likely to benefit from receiving treatment. These patients can be prioritized in situations where supply or logistical constraints make it impossible to offer therapy to all eligible patients. Both the Pediatric Infectious Diseases Society and the American Academy of Pediatrics advocate for a risk-stratified approach to identifying the patients who are at the highest risk of progression to severe COVID-19 among those eligible for therapies under Food and Drug Administration (FDA) Emergency Use Authorizations (EUAs).[5,7]

The Panel's approach to risk stratification and prioritization considers COVID-19 vaccination status, immune function, clinical risk factors, the strength of the evidence that demonstrates an association between each clinical risk factor and severe disease, and expert opinion.[6,8-21] See Special Considerations in Children for more information on clinical risk factors. The Panel suggests that decisions regarding treatment be individualized, particularly for patients in the intermediate risk category. Clinicians should consider the number and severity of comorbid conditions, the child's vaccination status, and the time since vaccination.

Comorbid conditions associated with severe COVID-19 are separated into the following categories in Table 3b:

- *Strong or Consistent Association With Progression to Severe COVID-19:* Comorbid conditions for which the published literature most consistently supports an increased risk of severe COVID-19. Patients in this category are moderately or severely immunocompromised, at risk of severe COVID-19, and not expected to develop an adequate immune response to COVID-19 vaccination.
- *Moderate or Inconsistent Association With Progression to Severe COVID-19:* Comorbid conditions and ages for which the published literature supports an association with severe COVID-19, but the association may be moderate or inconsistent across studies. In addition, the absolute risk of progression to severe disease or death is likely modest for any of the patients in this category.
- *Weak or Unknown Association With Progression to Severe COVID-19:* Comorbid conditions for which the data suggesting an association with severe COVID-19 are weak or for which an association is unknown. Patients with no comorbidities are included in this category.

Vaccination Status

Because COVID-19 vaccines are highly effective in preventing severe disease, individuals who are not immunocompromised and are up to date on their vaccines (i.e., those who have received the recommended booster dose[s], if eligible, or who have completed the primary series but are not yet eligible for a booster)[22] are likely to have a low absolute risk of severe disease. Therefore, the potential benefit from antiviral treatment is less clear for these patients. Patients who have had the primary series of vaccinations (i.e., those who are fully vaccinated but not up to date) may have a lower level of protection against severe disease than patients who are up to date, but the data comparing these groups are limited. However, evidence suggests that vaccine protection against severe COVID-19 wanes over time, particularly protection against the Omicron variant of concern (VOC) and its subvariants.[23-26] Clinicians should consider the time since a child's vaccination when making treatment decisions.

Health Disparities

COVID-19–related outcomes are worse among medically underserved populations, although this factor is not strictly a comorbid condition. Some racial and ethnic groups experience disproportionate rates of COVID-19 hospitalization and are less likely to receive specific therapies.[27-30] These factors may be relevant when making clinical decisions about treatment.[31,32] See Special Considerations in Children for more information.

Rationale for the Panel's Recommendations

Ritonavir-Boosted Nirmatrelvir (Paxlovid)

Ritonavir-boosted nirmatrelvir has received an FDA EUA for the treatment of mild to moderate COVID-19 in nonhospitalized adolescents aged ≥12 years and weighing ≥40 kg who are at high risk of progression to severe COVID-19.[33]

The EPIC-HR trial enrolled adults aged ≥18 years who were at high risk of severe COVID-19; they were randomized to receive ritonavir-boosted nirmatrelvir or placebo. The primary outcome of COVID-19–related hospitalization or all-cause mortality occurred in 8 of 1,039 patients (0.8%) who received ritonavir-boosted nirmatrelvir and in 66 of 1,046 patients (6.3%) who received placebo, an 89% relative risk reduction.[34] No pediatric patients were included in the trial, and no pediatric safety data were made available.

Ritonavir has been used extensively in pediatric patients as a pharmacokinetic booster for the treatment of HIV and hepatitis C virus infection, and it has a known and tolerable side effect profile. In the FDA EUA, the dose of ritonavir-boosted nirmatrelvir authorized for adolescents aged ≥12 years and weighing ≥40 kg is expected to result in a drug exposure similar to that observed in adults.[33]

Given the high efficacy of ritonavir-boosted nirmatrelvir in adults, its overall manageable side effect profile, the pediatric clinical experience with ritonavir, and the convenience of an oral medication, the Panel recommends the use of **ritonavir-boosted nirmatrelvir (Paxlovid)** for nonhospitalized adolescents aged ≥12 years and weighing ≥40 kg who have mild to moderate COVID-19 and are at the highest risk of progression to severe COVID-19 **(BIII)**. Ritonavir-boosted nirmatrelvir is expected to be active against all Omicron subvariants, although clinical efficacy data are currently limited.[35-37]

Because of the potential for significant drug-drug interactions with some concomitant medications, ritonavir-boosted nirmatrelvir may not be the safest choice for some patients. See Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications for more information.

Remdesivir

Remdesivir is approved by the FDA for use in hospitalized and nonhospitalized pediatric patients aged ≥28 days and weighing ≥3.0 kg.[38] Remdesivir is expected to be active against the Omicron VOC and its subvariants, although clinical efficacy data are currently limited.[37,39-41]

In a study that included nonhospitalized adults with mild to moderate COVID-19 who were at high risk of progression to severe disease, administering an intravenous (IV) infusion of remdesivir once daily for 3 days resulted in an 87% relative reduction in the risk of hospitalization or death when compared with placebo.[42] Although adolescents aged ≥12 years were eligible for inclusion, the trial included only 8 patients aged <18 years; therefore, no conclusions regarding the efficacy of remdesivir in children can be made from this trial. In addition, clinical experience data from hospitalized children with COVID-19 who received remdesivir through a compassionate use program have been reported.[2,43] Given the demonstrated efficacy of remdesivir in the overall study population, its overall favorable side effect profile, and clinical experience with remdesivir in hospitalized children, **remdesivir**, as an alternative to ritonavir-boosted nirmatrelvir, can be considered for children aged ≥12 years who are at the highest risk of progression to severe COVID-19 **(CIII)**.

There is insufficient evidence to recommend either for or against the routine use of remdesivir for the treatment of COVID-19 in nonhospitalized children aged <12 years who are at the highest risk of progression to severe disease or who are at intermediate risk of severe disease. Administering remdesivir requires performing an IV infusion once daily for 3 days, so logistical constraints may preclude the use of remdesivir in many settings.

Pharmacologic Therapies Not Recommended for Nonhospitalized Children With COVID-19

Molnupiravir

The FDA EUA for molnupiravir is limited to people aged ≥18 years, and there are no data on the safety of using molnupiravir in children.[44] The mechanism of action of molnupiravir has raised concerns about potential mutagenesis in mammalian cells. See Molnupiravir and Therapeutic Management of Nonhospitalized Adults With COVID-19 for additional information.

Corticosteroids

Corticosteroids are not indicated for the treatment of COVID-19 in nonhospitalized children. However, corticosteroids should be used per usual standards of care in children with asthma and croup triggered by SARS-CoV-2 infection. Children with COVID-19 who are receiving corticosteroids for an underlying condition should continue this therapy as directed by their health care providers.

Other Therapeutic Agents

For other therapies that have been studied or are under investigation for the treatment of COVID-19, see Therapies.

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Therapeutic Management of Hospitalized Children With COVID-19

Last Updated: August 8, 2022

This section outlines the COVID-19 Treatment Guidelines Panel's (the Panel) recommendations for the therapeutic management of children (i.e., pediatric patients aged <18 years) who are hospitalized for COVID-19. Throughout this section, the term "COVID-19" refers to the acute, primarily respiratory illness due to infection with SARS-CoV-2. Multisystem inflammatory syndrome in children (MIS-C) refers to the postinfectious inflammatory condition.

Treatment Considerations for Children With COVID-19

Currently, no pediatric clinical trial results evaluating the treatment of COVID-19 have been published. Data evaluating pharmacologic therapy in children with COVID-19 are limited largely to descriptive reports.[1,2] Therefore, more high-quality randomized trials, observational studies, and pharmacokinetic studies are urgently needed. Whenever possible, clinical trials of therapeutics and multicenter observational cohorts should enroll children with COVID-19.

Published guidance documents on the treatment of COVID-19 in children have been mostly extrapolated from recommendations for adults with COVID-19, recommendations for children with other viral infections, and expert opinion.[3-5] Applying adult data from COVID-19 trials to children is a unique challenge because most children experience a mild course of illness with COVID-19. Relative to adults, children with COVID-19 have substantially lower mortality and less need for hospitalization. Because of these differences in epidemiology and disease severity, the effect sizes for children are likely to be smaller than those observed in adults; therefore, to produce a beneficial outcome, the number needed to treat is higher. Collectively, these factors influence the risk versus benefit balance for pharmacologic therapies in children.

Other challenges are the uncertainty about which comorbid conditions place children at the highest risk of severe COVID-19 and the uncertainty about the absolute magnitude of the increased risk from those comorbid conditions. For children with COVID-19, the number and severity of their comorbid conditions influence decisions about pharmacologic treatment. For more information on risk factors for children with COVID-19, see Special Considerations in Children.

Recommendations

In the absence of sufficient clinical trial data on the treatment of children with COVID-19, the Panel's recommendations for the therapeutic management of hospitalized children are based largely on adult safety and efficacy data from clinical trials, the child's risk of disease progression, and expert opinion (see Table 3c). For the Panel's recommendations for adults, see Therapeutic Management of Hospitalized Adults With COVID-19.

In general, adult data are most applicable to older children with severe COVID-19 and predominantly lower respiratory tract disease. Extrapolation of adult data to children with SARS-CoV-2 infection who present with clinical syndromes common to other respiratory viruses (e.g., bronchiolitis, croup, asthma) is challenging. No evidence indicates that these syndromes should be managed differently when caused by SARS-CoV-2 infection. Clinical judgment is needed when applying these recommendations to patients, particularly young children.

Table 3c. Therapeutic Management of Hospitalized Children With COVID-19

Disease Severity	Panel's Recommendations
Hospitalized for COVID-19	For children aged ≥12 years admitted for COVID-19, use prophylactic anticoagulation unless contraindicated **(BIII)**.
Does Not Require Supplemental Oxygen	For children admitted for COVID-19 who are at the highest risk of progression to severe COVID-19,[a] consider using **remdesivir**[b] for children aged 12–17 years **(CIII)**. There is insufficient evidence for using remdesivir in children aged 28 days to <12 years.
	For children admitted for reasons other than COVID-19 who have mild to moderate COVID-19 and are at the highest risk of progression,[a] refer to Therapeutic Management of Nonhospitalized Children With COVID-19.
Requires Conventional Oxygen[c]	Use 1 of the following options: • **Remdesivir**[b] **(BIII)** • **Dexamethasone plus remdesivir**[b] for children with increasing oxygen needs, particularly adolescents **(BIII)**
Requires Oxygen Through High-Flow Device or NIV[d]	Use 1 of the following options: • **Dexamethasone (BIII)** • **Dexamethasone plus remdesivir**[b] **(BIII)**
	For children who do not have rapid (e.g., within 24 hours) improvement in oxygenation after initiation of dexamethasone, **baricitinib**[e] or **tocilizumab** can be considered for children aged 12–17 years **(BIII)** and for children aged 2–11 years **(CIII)**.
Requires MV or ECMO[f]	**Dexamethasone**[f] **(AIII)**
	For children who do not have rapid (e.g., within 24 hours) improvement in oxygenation after initiation of dexamethasone, **baricitinib**[e] or **tocilizumab** may be considered for children aged 12–17 years **(BIII)** and for children aged 2–11 years **(CIII)**.
Each recommendation in the Guidelines receives 2 ratings that reflect the strength of the recommendation and the quality of the evidence that supports it. See Guidelines Development for more information.	

[a] For example, for children who are severely immunocompromised regardless of COVID-19 vaccination status and those who are unvaccinated and have additional risk factors for progression (see Therapeutic Management of Nonhospitalized Children With COVID-19).

[b] The clinical benefit of remdesivir is greatest if it is initiated within 10 days of symptom onset. Remdesivir should be given for 5 days or until hospital discharge, whichever comes first.

[c] Conventional oxygen refers to oxygen supplementation that is not high-flow oxygen, NIV, MV, or ECMO.

[d] Patients who are receiving NIV or MV at baseline and require a substantial increase in baseline support should be treated per the recommendations for patients requiring new NIV or MV.

[e] **Tofacitinib** is an alternative if baricitinib is not available **(BIII)**.

[f] For children who started receiving remdesivir before admission to the ICU, the remdesivir should be continued to complete the treatment course.

Key: ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; MV = mechanical ventilation; NIV = noninvasive ventilation

Rationale for the Panel's Recommendations for Drug Therapies

Remdesivir

Remdesivir is approved by the Food and Drug Administration (FDA) for hospitalized and nonhospitalized pediatric patients aged ≥28 days and weighing ≥3 kg.[6] Remdesivir is expected to be active against the Omicron variant of concern, although in vitro and in vivo data are currently limited (see Remdesivir).[7] For most hospitalized patients, remdesivir should be administered for 5 days or until the patient is ready for discharge, whichever comes first. Treatment may be extended to 10 days for severely ill patients who have not clinically improved or for patients who are severely immunocompromised.

In a trial conducted predominantly among hospitalized patients with COVID-19 who did not receive supplemental oxygen at enrollment, a 5-day course of remdesivir was associated with greater clinical improvement when compared with the standard of care.[8] Remdesivir was also studied in ACTT-1, a double-blind, placebo-controlled, randomized trial for hospitalized adults with COVID-19 who received remdesivir for 10 days (or until hospital discharge) or placebo.[9] The study reported that the remdesivir arm had a shorter time to clinical recovery than the placebo arm (10 days vs. 15 days; $P < 0.001$). A subgroup analysis demonstrated that patients who received conventional oxygen therapy had the greatest benefit. No benefit was detected for patients who did not receive supplemental oxygen or for those who received noninvasive ventilation (NIV) or mechanical ventilation. No statistically significant differences in mortality or in the need for new mechanical ventilation were detected, and the benefit of remdesivir in this study was limited to patients with symptoms for <10 days.

Three open-label trials in adults compared remdesivir to a local standard of care.[10,11] The World Health Organization's Solidarity trial enrolled hospitalized adult patients with COVID-19 in 35 countries. In the overall cohort, no difference in hospital mortality was demonstrated (14.5% in the remdesivir arm vs. 15.6% in the usual care arm; rate ratio 0.91; 95% CI, 0.82–1.02; $P = 0.12$). However, in the subset of patients receiving supplemental oxygen but not NIV or mechanical ventilation, remdesivir significantly reduced the risk of in-hospital mortality by 13% (14.6% vs. 16.3%; rate ratio 0.87; 95% CI, 0.76–0.99; $P = 0.03$).[10]

The CATCO study demonstrated similar findings. Treatment with remdesivir, when compared with standard care, reduced the need for mechanical ventilation in hospitalized adults with COVID-19 (8% vs. 15%; relative risk 0.53; 95% CI, 0.38–0.75). In this study, 87% of patients in both the remdesivir arm and standard of care arm received dexamethasone.[12] In contrast to these 2 studies, the DisCoVeRy trial demonstrated no difference for any clinical outcome when the use of remdesivir plus usual care was compared to usual care alone.[11]

The efficacy of remdesivir has not been evaluated in clinical trials of hospitalized children with COVID-19. A Phase 2/3, single-arm, open-label study evaluated the safety, tolerability, and pharmacokinetics of remdesivir in 53 hospitalized children with COVID-19.[13] Children weighing 3 kg to <40 kg received remdesivir 5 mg/kg on Day 1, followed by remdesivir 2.5 mg/kg daily. Adverse events included acute kidney injury (11%) and an increase in alanine transaminase levels (8%). However, this study did not have a placebo group, limiting the ability to draw conclusions regarding the significance of these adverse events. Published observational data are limited to descriptive case series.[1,2]

Findings from the adult trials and the pediatric pharmacokinetic study led the Panel to recommend **remdesivir** for hospitalized children who require conventional oxygen **(BIII)** and to recommend **remdesivir** with **dexamethasone** for children with increasing need for conventional oxygen **(BIII)**. The Panel also recommends **remdesivir** in combination with **dexamethasone** for children who require oxygen through a high-flow device or NIV **(BIII)**. It is not known if remdesivir offers an additional

clinical benefit to standard care in younger children with SARS-CoV-2 infection who are receiving respiratory support for bronchiolitis, asthma, or croup.

For children hospitalized for COVID-19 who do not require supplemental oxygen, the Panel recommends **remdesivir** for children aged 12 to 17 years who are at the highest risk for progression to severe disease **(CIII)**. This recommendation was extrapolated from the findings of the PINETREE study, which demonstrated a reduction in hospitalization among high-risk, unvaccinated adults treated in the outpatient setting.[14] However, there is insufficient evidence for or against the use of remdesivir in children aged 28 days to <12 years and weighing ≥3 kg who do not require supplemental oxygen. Given the reported clinical experience with the use of remdesivir among younger patients,[13] the use of remdesivir in high-risk, younger children who do not require supplemental oxygen may be considered on a case-by-case basis.

Dexamethasone

Dexamethasone was evaluated in the RECOVERY trial, which was an open-label, randomized trial conducted in the United Kingdom.[15] The trial compared the use of up to 10 days of dexamethasone 6 mg, administered by intravenous injection or orally, with usual care among hospitalized adults with COVID-19. The primary outcome was all-cause mortality at 28 days, which occurred in 22.9% of patients randomized to receive dexamethasone versus 25.7% of patients randomized to receive usual care (age-adjusted rate ratio 0.83; 95% CI, 0.75–0.93; $P < 0.001$). Patients who required mechanical ventilation or extracorporeal membrane oxygenation (ECMO) had the greatest effect size (29.3% vs. 41.4%; rate ratio 0.64; 95% CI, 0.51–0.81). No difference in outcomes was observed for patients who did not require supplemental oxygen (17.8% vs. 14.0%; rate ratio 1.19; 95% CI, 0.92–1.55). For the 28-day mortality outcome, a difference between arms was observed for patients who required supplemental oxygen (23.3% vs. 26.2%; rate ratio 0.82; 95% CI, 0.72–0.94). However, it should be noted that these patients were a heterogeneous group, including those who received either conventional oxygen or NIV. See Corticosteroids for detailed information.

The safety and efficacy of using dexamethasone or other corticosteroids for the treatment of COVID-19 have not been evaluated in pediatric patients. Given that the mortality for adults in the placebo arm in the RECOVERY trial was substantially greater than the mortality generally reported for children with COVID-19, caution is warranted when extrapolating from recommendations for adults and applying them to patients aged <18 years.

However, because of the effect size observed in the RECOVERY trial, the Panel recommends the use of **dexamethasone** for children who require mechanical ventilation or ECMO **(AIII)**. The Panel also recommends the use of **dexamethasone**, with or without concurrent remdesivir, for children who require oxygen through a high-flow device or NIV **(BIII)**. The Panel **does not recommend** routine use of **corticosteroids** for children who require only conventional oxygen, but corticosteroids can be considered in combination with remdesivir for patients with increasing oxygen needs, particularly adolescents **(BIII)**.

There is evidence demonstrating that the use of corticosteroids does not benefit infants with viral bronchiolitis not related to COVID-19, and current American Academy of Pediatrics guidelines recommend against the use of corticosteroids in this population.[16] There are no COVID-19-specific data to support the use of corticosteroids in children with bronchiolitis due to SARS-CoV-2 infection. Corticosteroids should be used per the usual standards of care in children with asthma and croup triggered by SARS-CoV-2.

The use of dexamethasone for the treatment of severe COVID-19 in children who are profoundly immunocompromised has not been evaluated, and there is a potential risk of harm. Therefore, the

use of corticosteroids should be considered on a case-by-case basis in consultation with relevant specialists, and the benefits and risks of the therapy should be weighed. If dexamethasone is not available, alternative glucocorticoids such as prednisone, methylprednisolone, or hydrocortisone can be considered. The dexamethasone dose for pediatric patients is 0.15 mg/kg (with a maximum dose of 6 mg) once daily for ≤10 days.

Baricitinib

The Janus kinase inhibitor baricitinib was recently approved by the FDA for the treatment of COVID-19 in hospitalized adults. An FDA Emergency Use Authorization (EUA) for baricitinib remains active for the treatment of COVID-19 in hospitalized children aged 2 to 17 years who require supplemental oxygen, NIV, mechanical ventilation, or ECMO.[17]

In the COV-BARRIER trial, adults with COVID-19 pneumonia were randomized to receive baricitinib or standard care. Patients treated with baricitinib showed a reduction in mortality when compared with those who received standard care; the reduction was greatest in patients who received high-flow oxygen or NIV. Similarly, the ACTT-2 trial in adults showed that patients who received baricitinib plus remdesivir had improved time to recovery when compared with patients who received remdesivir alone. This effect was most pronounced in patients who received high-flow oxygen or NIV.[18] In the ACTT-4 trial, 1,010 patients were randomized 1:1 to receive baricitinib plus remdesivir or dexamethasone plus remdesivir. The study reported no difference between the arms for the outcome of mechanical ventilation-free survival.[19]

In the RECOVERY trial, 8,156 patients, including 33 children aged 2 to 17 years, were randomized to receive baricitinib or usual care (95% received corticosteroids).[20] Treatment with baricitinib was associated with a 13% proportional reduction in mortality, with the greatest effect size occurring in patients who received NIV. The RECOVERY investigators included these patients in a meta-analysis and found that treatment with baricitinib was associated with a 20% proportional reduction in mortality (rate ratio 0.80; 95% CI, 0.72–0.89; $P < 0.0001$). See Kinase Inhibitors: Janus Kinase Inhibitors and Bruton's Tyrosine Kinase Inhibitors and Therapeutic Management of Hospitalized Adults With COVID-19 for additional information. These data in adults indicate that baricitinib is likely to be most beneficial for patients receiving noninvasive forms of respiratory support.

Several open-label trials and cohort studies have evaluated baricitinib in children with autoinflammatory and rheumatic diseases, including many children aged <5 years, and found the treatment was well tolerated; however, the pharmacokinetics of baricitinib in younger children are not well studied.[21-24] Information on the safety and effectiveness of the use of baricitinib in children with COVID-19 is limited to case reports.

In contrast to the strong recommendation for its use for adults, baricitinib is not considered the standard of care for all children who require high-flow oxygen or NIV because of the low mortality in children with COVID-19 (especially in young children) and the limited data on the use of baricitinib in these children.

Extrapolating from clinical trials among adults with COVID-19, the Panel recommends that:

- For children who require oxygen through a high-flow device or NIV *and* do not have rapid (e.g., within 24 hours) improvement in oxygenation after initiation of dexamethasone, **baricitinib** can be considered for children aged 12 to 17 years **(BIII)** and for children aged 2 to 11 years **(CIII)**.
- For children who require mechanical ventilation or ECMO *and* do not have rapid (e.g., within 24 hours) improvement in oxygenation after initiation of dexamethasone, **baricitinib** may be considered for children aged 12 to 17 years **(BIII)** and for children aged 2 to 11 years **(CIII)**.

Clinicians should consult with specialists experienced in treating children with immunosuppression (e.g., with pediatric infectious disease, pediatric rheumatology) when considering administering baricitinib to hospitalized children with COVID-19. Data from adults indicate that baricitinib should be initiated promptly; ideally, it should be initiated at the onset of clinical deterioration or respiratory failure.

Tofacitinib

There are no data on the efficacy of tofacitinib in pediatric patients with COVID-19; the Panel's recommendation is extrapolated from data in adults. The STOP-COVID trial compared tofacitinib to the standard of care in adults hospitalized for COVID-19 pneumonia.[25] The standard of care included glucocorticoids for most patients. The study demonstrated a reduction in mortality and respiratory failure at Day 28 for the tofacitinib arm when compared with the placebo arm. Tofacitinib has been studied less extensively than baricitinib for the treatment of COVID-19. Thus, tofacitinib, as an alternative to baricitinib, is recommended to be used in combination with dexamethasone in adults with COVID-19 who require high-flow oxygen or NIV. See Kinase Inhibitors: Janus Kinase Inhibitors and Bruton's Tyrosine Kinase Inhibitors and Therapeutic Management of Hospitalized Adults With COVID-19 for additional information.

No trials have evaluated the safety of using tofacitinib in children with COVID-19. Overall, there has been more clinical experience with the use of tofacitinib than baricitinib in children, particularly when used in children with juvenile idiopathic arthritis (JIA) as young as 2 years of age. A Phase 1 study was conducted to define the pharmacokinetics and safety of using tofacitinib in children,[26] and a Phase 3, double-blind, randomized, placebo-controlled trial investigated the efficacy of using tofacitinib in children with JIA.[27] Tofacitinib is available as a liquid formulation for children.

Given the established safety of tofacitinib in the pediatric population, **tofacitinib** can be considered an alternative for children hospitalized for COVID-19 if baricitinib is not available **(BIII)**. The dose of tofacitinib that should be used to treat hospitalized children with COVID-19 has not been established. As with baricitinib, the dose of tofacitinib for hospitalized children with COVID-19 likely needs to be higher than the dose typically used to treat pediatric rheumatologic diseases. Therefore, clinicians should consult with specialists experienced in treating children with immunosuppression (e.g., with pediatric infectious disease, pediatric rheumatology) when considering administering tofacitinib to hospitalized children with COVID-19.

Tocilizumab

Tocilizumab is an interleukin (IL)-6 inhibitor that has received an FDA EUA for the treatment of hospitalized adults and children with COVID-19 who are aged ≥2 years, receiving systemic corticosteroids, and require supplemental oxygen, NIV, mechanical ventilation, or ECMO.[28] Two large randomized controlled trials (REMAP-CAP and RECOVERY) conducted among hospitalized adults with COVID-19 have demonstrated reductions in mortality with the use of tocilizumab. See Interleukin-6 Inhibitors and Therapeutic Management of Hospitalized Adults With COVID-19 for additional information.

The RECOVERY trial was an open-label study that included hospitalized adults who had an oxygen saturation of <92% on room air or were receiving supplemental oxygen therapy; patients also had C-reactive protein levels ≥75 mg/L.[29] Patients were randomized to receive tocilizumab plus usual care or usual care alone. Mortality at 28 days was significantly lower in the tocilizumab arm compared to the usual care arm. The REMAP-CAP trial included adults with suspected or confirmed COVID-19 who were admitted to an intensive care unit and received either respiratory (i.e., NIV or mechanical ventilation) or cardiovascular organ (i.e., vasopressor/inotrope) support.[30] Patients were randomized within 24

hours of organ failure to receive either tocilizumab or sarilumab (the majority received tocilizumab) or to receive standard care. The median number of organ support-free days was higher for those who received tocilizumab than for those who received standard care, and in-hospital mortality was lower in the combined tocilizumab or sarilumab arm than in the standard care arm. In both studies, the majority of patients received dexamethasone (82% in the RECOVERY trial and 93% in the REMAP-CAP trial).

Studies have evaluated the use of tocilizumab for the treatment of non-COVID-19 conditions in children, including JIA[31-35] and chimeric antigen receptor T cell-related cytokine release syndrome.[36] The FDA approved tocilizumab for use in children aged ≥2 years for these indications.[31-35] The use of tocilizumab for children with severe cases of COVID-19 has been described only in case series.[37-39]

Extrapolating from clinical trials among adults with COVID-19, the Panel recommends that:

- For children who require oxygen through a high-flow device or NIV *and* who do not have rapid (e.g., within 24 hours) improvement in oxygenation after initiation of dexamethasone, **tocilizumab** can be considered for children aged 12 to 17 years **(BIII)** and for children aged 2 to 11 years **(CIII)**.
- For children who require mechanical ventilation or ECMO *and* who do not have rapid (e.g., within 24 hours) improvement in oxygenation after initiation of dexamethasone, if tocilizumab has not been started, addition of **tocilizumab** may be considered for children aged 12 to 17 years **(BIII)** and for children aged 2 to 11 years **(CIII)**.

Data from REMAP-CAP and RECOVERY are most likely to be applicable to high-risk adolescent patients. Clinicians should consult with specialists experienced in treating children with immunosuppression (e.g., with pediatric infectious disease, pediatric rheumatology) when considering the use of tocilizumab in younger children with COVID-19.

Sarilumab

Sarilumab, a monoclonal antibody that blocks IL-6 receptors, is not authorized by the FDA for the treatment of COVID-19. Data evaluating the efficacy of sarilumab for the treatment of COVID-19 hyperinflammation are limited, and there is a lack of pediatric dosing information. Therefore, the Panel **recommends against** the use of **sarilumab** in hospitalized children with COVID-19, except in a clinical trial **(AIII)**.

Anticoagulation for Children With COVID-19

Limited data characterize the risk of thromboembolic disease in children with COVID-19. In a multicenter, retrospective cohort study that included 814 pediatric patients with COVID-19 or MIS-C,[40] thromboembolic events were detected in 2.1% of patients with COVID-19 and in 6.5% of patients with MIS-C. No trials to define the optimal approach to anticoagulation have been conducted among children. Therefore, the Panel recommends prophylactic anticoagulation for children aged ≥12 years who are hospitalized for COVID-19, unless there are contraindications **(BIII)**. There is insufficient evidence for the Panel to recommend either for or against anticoagulation in younger hospitalized children with COVID-19, although institutional standards for anticoagulation should be followed. There is insufficient evidence for the Panel to recommend either for or against high-intensity anticoagulation for children of any age with COVID-19.

Other Therapeutic Agents

For other therapies that have been studied or are under investigation for the treatment of COVID-19, see Therapies.

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

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

Multisystem Inflammatory Syndrome in Adults

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

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

Patient Condition	Panel's Recommendations

MIS-C	**Initial treatment for MIS-C includes both immunomodulatory and antithrombotic therapy.**
	Initial Immunomodulatory Therapy
	• **IVIG** 2 g/kg IBW/dose (up to a maximum total dose of 100 g)[a] IV **plus** low-to-moderate dose **methylprednisolone** (1–2 mg/kg/day) IV[a] or another glucocorticoid at an equivalent dosea **(AIIb)**.
	• The Panel recommends against the routine use of IVIG monotherapy for the treatment of MIS-C unless glucocorticoid use is contraindicated **(AIIb)**.
	Intensification Immunomodulatory Therapy
	• For children with refractory MIS-C who do not improve within 24 hours of initial immunomodulatory therapy, start 1 of the following (listed in alphabetical order) **(AIII)**:
	  • High-dose **anakinra** 5–10 mg/kg IV or SUBQ daily **(BIIb)**, *or*
	  • **Higher-dose glucocorticoid** (e.g., **methylprednisolone** 10–30 mg/kg/day IV or equivalent glucocorticoid) **(BIIb)**,[b] *or*
	  • **Infliximab**[c] 5–10 mg/kg IV for 1 dose **(BIIb)**.
	Antithrombotic Treatment
	• Low-dose **aspirin** (3–5 mg/kg/day, up to maximum daily dose of 81 mg) PO for all patients without risk factors for bleeding **(AIII)**, **AND**
	• Anticoagulation for patients who fall under 1 of the following clinical scenarios:
	  • **Therapeutic anticoagulation** for patients with large CAAs according to the American Heart Association guidelines for Kawasaki disease **(AIII)**.
	  • **Therapeutic anticoagulation** for patients with moderate to severe LV dysfunction who have no risk factors for bleeding **(AIII)**.
	  • For patients with MIS-C who do not have large CAAs or moderate to severe LV dysfunction, consider **prophylactic or therapeutic anticoagulation** on an individual basis, taking into consideration risk factors for thrombosis. See Table 3e for additional information.

Each recommendation in the Guidelines receives 2 ratings that reflect the strength of the recommendation and the quality of the evidence that supports it. See Guidelines Development for more information.	

[a] Duration of therapy may vary. See duration in table and text below.

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

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

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

Table 3e. Dosing Regimens for the Drugs Recommended for the Treatment of MIS-C

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

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

Treatment Considerations for Children With MIS-C

Initial Immunomodulatory Therapy for MIS-C

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

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

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

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

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

Intravenous Immunoglobulin in Combination With Glucocorticoids

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

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

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

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

Intravenous Immunoglobulin Monotherapy

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

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

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

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

Glucocorticoid Monotherapy

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

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

Intensification Immunomodulatory Therapy for MIS-C

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

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

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

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

High-Dose Glucocorticoids

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

Anakinra

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

Infliximab

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

Antithrombotic Treatment for MIS-C

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

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

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

Antiviral Therapy in MIS-C

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

Critical Care Management

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

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Care of Critically Ill Adults With COVID-19

Last Updated: May 31, 2022

Summary Recommendations

Hemodynamics

- For adults with COVID-19 and shock, the COVID-19 Treatment Guidelines Panel (the Panel) recommends using dynamic parameters, skin temperature, capillary refilling time, and/or lactate levels over static parameters to assess fluid responsiveness **(BIIa)**.
- For the acute resuscitation of adults with COVID-19 and shock, the Panel recommends using buffered/balanced crystalloids over unbalanced crystalloids **(BIIa)**.
- For the acute resuscitation of adults with COVID-19 and shock, the Panel **recommends against** the initial use of **albumin** for resuscitation **(BI)**.
- For adults with COVID-19 and shock, the Panel recommends **norepinephrine** as the first-line vasopressor **(AI)**.
- For adults with COVID-19 and shock, the Panel recommends titrating vasoactive agents to target a mean arterial pressure (MAP) of 60 to 65 mm Hg over higher MAP targets **(BI)**.
- The Panel **recommends against** using **hydroxyethyl starches** for intravascular volume replacement in adult patients with COVID-19 and sepsis or septic shock **(AI)**.
- When norepinephrine is available, the Panel **recommends against** using **dopamine** for adult patients with COVID-19 and shock **(AI)**.
- As a second-line vasopressor, the Panel recommends adding either **vasopressin** (up to 0.03 units/min) **(BIIa)** or **epinephrine (BIIb)** to norepinephrine to raise MAP to target or adding **vasopressin** (up to 0.03 units/min) **(BIIa)** to decrease norepinephrine dosage.
- The Panel **recommends against** using **low-dose dopamine** for renal protection **(AI)**.
- The Panel recommends using **dobutamine** in adult patients with COVID-19 who show evidence of cardiac dysfunction and persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents **(BIII)**.
- The Panel recommends that all adult patients with COVID-19 who require vasopressors have an arterial catheter placed as soon as practical, if the resources to do so are available **(BIII)**.
- For adult patients with refractory septic shock who have completed a course of corticosteroids to treat COVID-19, the Panel recommends using **low-dose corticosteroid therapy** ("shock-reversal") over no corticosteroid therapy **(BIIa)**.

Oxygenation and Ventilation

- For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy, the Panel recommends starting therapy with high-flow nasal cannula (HFNC) oxygen; if patients fail to respond, noninvasive ventilation (NIV) or intubation and mechanical ventilation should be initiated **(BIIa)**.
- For adults with COVID-19 and acute hypoxemic respiratory failure who do not have an indication for endotracheal intubation and for whom HFNC oxygen is not available, the Panel recommends performing a closely monitored trial of NIV **(BIIa)**.
- For adults with persistent hypoxemia who require HFNC oxygen and for whom endotracheal intubation is not indicated, the Panel recommends a trial of awake prone positioning **(BIIa)**.
- The Panel **recommends against** the use of awake prone positioning as a rescue therapy for refractory hypoxemia to avoid intubation in patients who otherwise meet the indications for intubation and mechanical ventilation **(AIII)**.
- If intubation becomes necessary, the procedure should be performed by an experienced practitioner in a controlled setting due to the enhanced risk of exposing health care practitioners to SARS-CoV-2 during intubation **(AIII)**.
- For mechanically ventilated adults with COVID-19 and acute respiratory distress syndrome (ARDS):
  - The Panel recommends using low tidal volume (VT) ventilation (VT 4–8 mL/kg of predicted body weight) over higher VT ventilation (VT >8 mL/kg) **(AI)**.
  - The Panel recommends targeting plateau pressures of <30 cm H_2O **(AIIa)**.

Summary Recommendations, continued

- 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** (NMBAs) or a continuous **NMBA infusion** to facilitate protective lung ventilation **(BIIa)**.
  - In the event of persistent patient-ventilator dyssynchrony, or in cases where a patient requires ongoing deep sedation, prone ventilation, or persistently high plateau pressures, the Panel recommends using a continuous **NMBA infusion** for up to 48 hours, as long as the patient's anxiety and pain can be adequately monitored and controlled **(BIII)**.
- For mechanically ventilated adults with COVID-19, severe ARDS, and hypoxemia despite optimized ventilation and other rescue strategies:
  - The Panel recommends using recruitment maneuvers rather than not using recruitment maneuvers **(CIIa)**.
  - If recruitment maneuvers are used, the Panel **recommends against** using staircase (incremental PEEP) recruitment maneuvers **(AIIa)**.
  - The Panel recommends using an inhaled pulmonary vasodilator as a rescue therapy; if no rapid improvement in oxygenation is observed, the treatment should be tapered off **(CIII)**.

Pharmacologic Interventions

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

Extracorporeal Membrane Oxygenation

- There is insufficient evidence for the Panel to recommend either for or against the use of extracorporeal membrane oxygenation in adults with COVID-19 and refractory hypoxemia.

Each recommendation in the Guidelines receives 2 ratings that reflect the strength of the recommendation and the quality of the evidence that supports it. See Guidelines Development for more information.

Introduction to Critical Care Management of Adults With COVID-19

Last Updated: May 31, 2022

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

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

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

Selected Clinical Manifestations of COVID-19 Critical Illness

Inflammatory Response Due to COVID-19 in Adults

Patients with COVID-19 may express increased levels of pro-inflammatory cytokines and anti-inflammatory cytokines, which has previously been referred to as "cytokine release syndrome" or "cytokine storm." However, these terms are both imprecise and misnomers, because the magnitude of cytokine elevation in many patients with COVID-19 is modest compared to that in patients with many other critical illnesses, such as sepsis and ARDS.[2,3] In addition, some patients with elevated cytokine levels have no specific pathology that can be attributed to the elevated levels.

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

Multisystem Inflammatory Syndrome in Adults

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

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

Clinical Criteria

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

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

Laboratory Criteria

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

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

Because there is no specific diagnostic test for MIS-A, diagnosis of this inflammatory syndrome is one of exclusion after other causes (e.g., bacterial sepsis) have been eliminated. Although there are currently no controlled clinical trial data in patients with MIS-A to guide treatment of the syndrome, case reports have described the use of intravenous immunoglobulin, corticosteroids, or anti-IL-1 receptor antagonist therapy.[5-7]

COVID-19-Induced Cardiac Dysfunction, Including Myocarditis

The published literature describes cardiac injury or dysfunction in up to 24% of adults who are hospitalized with COVID-19.[8] COVID-19 may be associated with an array of cardiovascular

complications, including acute coronary syndrome, myocarditis, stress (Takotsubo) cardiomyopathy, arrythmias, and thromboembolic disease.[9]

Thromboembolic Events and COVID-19

Critically ill adults with COVID-19 have been observed to have a prothrombotic state and higher rates of venous thromboembolic disease. In some studies, thromboemboli have been diagnosed even in patients who received chemical prophylaxis with heparinoids.[10-12] Autopsy studies provide additional evidence of both thromboembolic disease and microvascular thrombosis in patients with COVID-19.[13] Some authors have called for routine surveillance of ICU patients for venous thromboembolism.[14] See Antithrombotic Therapy in Patients With COVID-19 for a more detailed discussion.

Renal and Hepatic Dysfunction Due to COVID-19

Although SARS-CoV-2 is primarily a pulmonary pathogen, renal and hepatic dysfunction are consistently described in adults with severe COVID-19.[15] In a 2020 multicenter cohort study of critically ill adults in the United States, 20.6% of patients developed acute kidney injury (AKI) that was treated with renal replacement therapy (RRT).[16] In a cohort of critically ill adults in Brazil, the development of an AKI that required RRT was associated with poor prognosis.[17]

Other Intensive Care Unit-Related Complications

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

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

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

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

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

Sedation Management in Adults With COVID-19

International guidelines provide recommendations on the prevention, detection, and treatment of pain, sedation, and delirium in ICU patients.[22,23] Sedation management strategies, such as maintaining a light level of sedation (when appropriate) and minimizing sedative exposure, have shortened the duration of mechanical ventilation and the length of stay in the ICU for patients without COVID-19.[24,25]

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

A. Assess, prevent, and manage pain;

B. Both spontaneous awakening and breathing trials;

C. Choice of analgesia and sedation;

D. Delirium: assess, prevent, and manage;

E. Early mobility and exercise; *and*

F. Family engagement and empowerment.

The A-F Bundle also provides frontline staff with practical application strategies for each element.[26] The A-F Bundle should be incorporated using an interprofessional team model. This approach helps standardize communication among team members, improves survival, and reduces long-term cognitive dysfunction of patients.[27] Despite the known benefits of the A-F Bundle, its impact has not been directly assessed in patients with COVID-19; however, use of the Bundle should be encouraged, when appropriate, to improve ICU patient outcomes. Prolonged mechanical ventilation of COVID-19 patients, coupled with deep sedation and potentially neuromuscular blockade, increases the workload of ICU staff. Additionally, significant drug shortages may force clinicians to use older sedatives with prolonged durations of action and active metabolites, impeding routine implementation of SCCM's PADIS guidelines. This puts patients at additional risk for ICU and post-ICU complications.

Post-Intensive Care Syndrome

Post-intensive care syndrome (PICS) is a spectrum of cognitive, psychiatric, and/or physical disability that affects survivors of critical illness and persists after a patient leaves the ICU.[28] Patients with PICS may present with varying levels of impairment, including profound muscle weakness (ICU-acquired weakness); problems with thinking and judgment (cognitive dysfunction); and mental health problems, such as problems sleeping, post-traumatic stress disorder (PTSD), depression, and anxiety. ICU-acquired weakness affects 33% of all patients who receive mechanical ventilation, 50% of patients with sepsis, and ≤50% of patients who remain in the ICU for ≥1 week.[29-31] Cognitive dysfunction affects 30% to 80% of patients discharged from the ICU.[32-34] About 50% of ICU survivors do not return to work within 1 year after discharge.[35] Although no single risk factor has been associated with PICS, there are opportunities to minimize the risk of PICS through medication management (using the A-F Bundle), physical rehabilitation, follow-up clinics, family support, and improved education about the syndrome. PICS also affects family members who participate in the care of their loved ones. In 1 study, a third of family members who had major decision-making roles experienced mental health problems, such as depression, anxiety, and PTSD.[36]

Some patients with COVID-19 who have been treated in the ICU express manifestations of PICS.[37] Although specific therapies for COVID-19-induced PICS are not yet available, physicians should maintain a high index of suspicion for cognitive impairment and other related problems in survivors of severe or critical COVID-19 illness.

Advance Care Planning and Goals of Care

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

To guide shared decision making in cases of serious illness, advance care planning should include identifying existing advance directives that outline a patient's preferences and values. Values and care

preferences should be discussed, documented, and revisited regularly for patients with or without prior directives. Specialty palliative care teams can facilitate communication between clinicians and surrogate 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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Hemodynamics for Adults

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Most of the hemodynamic recommendations below are similar to those previously published in the *Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016*. Ultimately, 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 7 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 (risk ratio 0.89; 95% CI, 0.81–0.98) and a lower risk of arrhythmias (risk ratio 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 2, 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 for Adults

Last Updated: September 26, 2022

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

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

Goal of Oxygenation

The optimal oxygen saturation measured by pulse oximetry (SpO_2) in adults with COVID-19 who are receiving supplemental oxygen is unknown. However, a target SpO_2 of 92% to 96% seems logical, considering that indirect evidence from patients without COVID-19 suggests that an SpO_2 of <92% or >96% may be harmful.[1,2] Special care should be taken when assessing SpO_2 in patients with darker skin pigmentation, as recent reports indicate that occult hypoxemia (defined as arterial oxygen saturation [SaO_2] <88% despite SpO_2 >92%) is more common in these patients.[3,4] See Clinical Spectrum of SARS-CoV-2 Infection for more information.

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 88% to 92%) or a liberal oxygen strategy (target SpO_2 ≥96%).[1] 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 14%; 95% CI, 0.7% to 27%), and a trend toward increased mortality was observed at Day 28 (between-group risk difference 8%; 95% CI, -5% to 21%).

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%.[2] This study found that a liberal oxygen supplementation strategy (a median fraction of inspired oxygen [FiO_2] of 0.52) was associated with an increased risk of in-hospital mortality (relative risk 1.21; 95% CI, 1.03–1.43) when compared to a more conservative SpO_2 supplementation strategy (a median FiO_2 of 0.21).

Acute Hypoxemic Respiratory Failure

In adults with COVID-19 and acute hypoxemic respiratory failure, conventional oxygen therapy may be insufficient to meet the oxygen needs of the patient. Options for providing enhanced respiratory support include using high-flow nasal canula (HFNC) oxygen, noninvasive ventilation (NIV), intubation and mechanical ventilation, or extracorporeal membrane oxygenation. In this section, mechanical ventilation refers to the delivery of positive pressure ventilation through an endotracheal or tracheostomy tube. NIV refers to the delivery of either continuous positive airway pressure (CPAP) or bilevel positive airway pressure (e.g., BiPAP) through a noninvasive interface, such as a face mask or nasal mask.

Nonmechanically Ventilated Adults With Acute Hypoxemic Respiratory Failure

High-Flow Nasal Cannula Oxygen and Noninvasive Ventilation

Recommendations

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

Rationale

HFNC oxygen is preferred over NIV in patients with acute hypoxemic respiratory failure. As there are no studies that directly compare the use of HFNC oxygen and NIV delivered by a mask in patients with COVID-19, this guidance is based on data from an unblinded clinical trial in patients without COVID-19 who had acute hypoxemic respiratory failure.[5] Study participants were randomized to receive HFNC oxygen, conventional oxygen therapy, or NIV. The patients in the HFNC oxygen arm had more ventilator-free days (mean 24 days) than those in the conventional oxygen therapy arm (mean 22 days) or the NIV arm (mean 19 days; $P = 0.02$). In addition, 90-day mortality was higher in both the conventional oxygen therapy arm (HR 2.01; 95% CI, 1.01–3.99) and the NIV arm (HR 2.50; 95% CI, 1.31–4.78) than in the HFNC oxygen arm. In the subgroup of severely hypoxemic patients (those with a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen [PaO_2/FiO_2] ≤200 mm Hg), the intubation rate was lower in the HFNC oxygen arm than in the conventional oxygen therapy arm or the NIV arm (HR 2.07 and 2.57, respectively).

The trial's findings were corroborated by a meta-analysis of 8 trials with 1,084 participants that assessed the effectiveness of oxygenation strategies.[6] Compared to NIV, HFNC oxygen reduced the rate of intubation (OR 0.48; 95% CI, 0.31–0.73) and intensive care unit (ICU) mortality (OR 0.36; 95% CI, 0.20–0.63).

One small study compared the use of NIV delivered by a helmet device to HFNC oxygen in patients with COVID-19. The HENIVOT trial randomized 109 patients with moderate or severe COVID-19 (defined as those who had PaO_2/FiO_2 <200 mm Hg) to receive either NIV via a helmet device or HFNC oxygen.[7] The study found no difference between the arms for the primary outcome of respiratory support-free days. However, only 30% of patients in the NIV arm required endotracheal intubation compared to 51% of patients in the HFNC oxygen arm ($P = 0.03$).

Two larger studies compared the use of NIV with conventional oxygen therapy in patients with COVID-19. The RECOVERY-RS trial was an adaptive randomized controlled trial that was essentially conducted as 2 separate trials that compared NIV and HFNC oxygen to the same conventional oxygen therapy control group.[8] The trial was stopped early and enrolled fewer than a third of the planned sample size of 4,002 participants. Between April 2020 and May 2021, 1,273 adults with COVID-19-related acute hypoxemic respiratory failure were randomized to receive NIV (n = 380), HFNC oxygen (n = 418), or conventional oxygen therapy (n = 475). The primary endpoint was a composite of endotracheal intubation or death within 30 days. The proportion of patients who met the primary endpoint was significantly lower in the NIV arm than in the conventional oxygen therapy arm (36.3% vs. 44.4%; $P = 0.03$). This difference was entirely due to a reduction in the number of patients who required intubation and not due to mortality. There was no significant difference between the HFNC oxygen arm and the conventional oxygen therapy arm in the occurrence of the primary endpoint (44.3% vs. 45.1%; $P = 0.83$).

There was substantial crossover between the arms, but an inverse probability weighting analysis that

corrected for the bias that this may have introduced did not change the results.[8] Adverse events were more common in the NIV arm. Initially, a comparison between NIV and HFNC oxygen was not planned, but a post hoc analysis found that the proportion of patients who required endotracheal intubation or died was lower in the NIV arm than in the HFNC oxygen arm (34.6% vs. 44.3%; $P = 0.02$).

In contrast to the RECOVERY-RS trial, the HiFlo-COVID trial randomized 220 patients with COVID-19 to receive HFNC oxygen or conventional oxygen therapy and found that a smaller proportion of patients in the HFNC oxygen arm required intubation (34.3% vs. 51.0%; $P = 0.03$).[9] Patients in the HFNC arm also had a shorter median time to recovery (11 vs. 14 days; $P = 0.047$).

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

NIV is an aerosol-generating procedure, and it may increase the risk of nosocomial transmission of SARS-CoV-2.[10,11] It remains unclear whether the use of HFNC oxygen results in a lower risk of nosocomial SARS-CoV-2 transmission than NIV.

Awake Prone Positioning in Nonmechanically Ventilated Adults

Recommendations

- For adults with persistent hypoxemia who require HFNC oxygen and for whom endotracheal intubation is not indicated, the Panel recommends a trial of awake prone positioning **(BIIa)**.
- The Panel **recommends against** the use of awake prone positioning as a rescue therapy for refractory hypoxemia to avoid intubation in patients who otherwise meet the indications for intubation and mechanical ventilation **(AIII)**.

Additional Considerations

- Patients who can adjust their position independently and tolerate lying prone can be considered for awake prone positioning.
- Awake prone positioning is acceptable and feasible for pregnant patients and can be performed in the left lateral decubitus position or the fully prone position.[12]
- Some patients do not tolerate awake prone positioning. Failure rates as high as 63% have been reported in the literature.[13]
- Awake prone positioning **should not be used** as a substitute for intubation and mechanical ventilation in patients with refractory hypoxemia who otherwise meet the indications for these interventions.
- Awake prone positioning may be infeasible or impractical in patients with:
  - Spinal instability
  - Facial or pelvic fractures
  - An open chest or unstable chest wall
- Awake prone positioning should be used with caution in patients with confusion, delirium, or hemodynamic instability; patients who cannot independently change position; or patients who

have had recent abdominal surgery, nausea, or vomiting.

Rationale

Awake prone positioning, or having a nonintubated patient lie on their stomach, may improve oxygenation and prevent the patient from progressing to requiring intubation and mechanical ventilation. Although prone positioning has been shown to improve oxygenation and outcomes in patients with moderate to severe ARDS who are receiving mechanical ventilation,[14,15] there is less evidence regarding the benefit of prone positioning in awake patients who require supplemental oxygen without mechanical ventilation. Several case series of patients with COVID-19 who required oxygen or NIV have reported that awake prone positioning improved oxygenation,[16-19] and some series have also reported low intubation rates after awake prone positioning.[16,18]

The Awake Prone Positioning Meta-Trial Group conducted the largest trial to date on awake prone positioning.[20] This was a prospective, multinational meta-trial of 6 open-label, randomized, controlled, superiority trials that compared awake prone positioning to standard care in adults who required HFNC oxygen for acute hypoxemic respiratory failure due to COVID-19.

The study enrolled 1,126 patients between April 2, 2020, and January 26, 2021, and the intention-to-treat analysis included 1,121 patients.[20] Of the 564 patients who underwent awake prone positioning, 223 (40%) met the primary composite endpoint of intubation or death within 28 days of enrollment. Among the 557 patients who received standard care, 257 (46%) met the primary endpoint (relative risk 0.86; 95% CI, 0.75−0.98). Regarding the individual components of the composite endpoint, the incidence of intubation by Day 28 was lower in the awake prone positioning arm than in the standard care arm (HR for intubation 0.75; 95% CI, 0.62−0.91). There was no difference in 28-day mortality between the awake prone positioning arm and the standard care arm (HR for mortality 0.87; 95% CI, 0.68−1.11).

During the first 14 days of the study, the median daily duration of awake prone positioning was 5.0 hours (IQR 1.6–8.8 hours).[20] However, the median daily duration varied from 1.6 hours to 8.6 hours across the individual trials. Longer daily durations for awake prone positioning were associated with treatment success by Day 28. This study evaluated the incidences of certain adverse events, including skin breakdown, vomiting, and central or arterial line dislodgment. These events occurred infrequently during the study, and the incidences for these events were similar between the arms. No cardiac arrests occurred during awake prone positioning.

The optimal daily duration of awake prone positioning is unclear. In a meta-trial of awake prone positioning, 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 when compared with 198 of 413 patients (48%) who remained in awake prone positioning for <8 hours per day.[20] This result 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.[14,15]

Intubation for Mechanical Ventilation

Recommendation

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

Rationale

It is essential to closely monitor hypoxemic patients with COVID-19 for signs of respiratory decompensation. To ensure the safety of both patients and health care workers, intubation should be

performed in a controlled setting by an experienced practitioner.

Mechanically Ventilated Adults

General Considerations

Recommendations

For mechanically ventilated adults with COVID-19 and ARDS:

- The Panel recommends using low tidal volume (VT) ventilation (VT 4–8 mL/kg of predicted body weight) over higher VT ventilation (VT >8 mL/kg) **(AI)**.
- The Panel recommends targeting plateau pressures of <30 cm H_2O **(AIIa)**.
- The Panel recommends using a conservative fluid strategy over a liberal fluid strategy **(BIIa)**.
- The Panel **recommends against** the routine use of **inhaled nitric oxide (AIIa)**.

Rationale

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

Positive End-Expiratory Pressure and Prone Positioning in Mechanically Ventilated Adults With Moderate to Severe ARDS

Recommendations

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

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

Rationale

PEEP is beneficial in patients with ARDS because it prevents alveolar collapse, improves oxygenation, and minimizes atelectotrauma, a source of ventilator-induced lung injury. A meta-analysis of individual patient data from the 3 largest trials that compared lower and higher levels of PEEP in patients without COVID-19 found lower rates of ICU mortality and in-hospital mortality with higher levels of PEEP in those with moderate (PaO_2/FiO_2 100–200 mm Hg) and severe (PaO_2/FiO_2 <100 mm Hg) ARDS.[21]

Although there is no clear standard as to what constitutes a high level of PEEP, a conventional threshold is >10 cm H_2O.[22] 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.[23,24] Other studies have reported that patients with moderate to severe ARDS due to COVID-19 had low lung compliance, similar to the lung compliance seen in patients with conventional ARDS.[25-28] These seemingly contradictory observations suggest that patients with COVID-19 and ARDS are a heterogeneous population, and assessments for responsiveness to higher levels of PEEP should be individualized based on oxygenation and lung compliance. Clinicians should monitor patients for known side effects of higher levels of PEEP, such as barotrauma and hypotension.

In the prepandemic PROSEVA study of patients with moderate or severe early ARDS (PaO_2/FiO_2 <150

mm Hg) who required mechanical ventilation, the patients who were randomized to undergo prone positioning for ≥16 hours per day had improved survival compared to those who remained in the supine position throughout their course of mechanical ventilation.[14] A meta-analysis evaluated the results of the PROSEVA study and 7 other randomized controlled trials that investigated the use of prone positioning in people with ARDS.[29] A subgroup analysis revealed that mortality was reduced among patients who remained prone for ≥12 hours per day when compared with patients who remained in the supine position (risk ratio 0.74; 95% CI, 0.56–0.99). Prone positioning improved oxygenation in all of the trials; patients in the prone positioning arms had higher PaO_2/FiO_2 on Day 4 than those in the supine positioning arms (mean difference 23.5 mm Hg; 95% CI, 12.4–34.5).

The use of prone positioning may be associated with serious adverse events, including unplanned extubation or central catheter removal. However, the meta-analysis found no differences between the prone positioning and supine positioning arms in the frequency of these events.[29] The use of prone positioning was associated with an increased risk of pressure sores (risk ratio 1.22; 95% CI, 1.06–1.41) and endotracheal tube obstruction (risk ratio 1.76; 95% CI, 1.24–2.50) in the 3 studies that evaluated these complications.

Neuromuscular Blockade in Mechanically Ventilated Adults With Moderate to Severe ARDS

Recommendations

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

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

Rationale

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

Rescue Therapies for Mechanically Ventilated Adults With ARDS

Recommendations

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

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

Rationale

A recruitment maneuver refers to a temporary increase in airway pressure during mechanical ventilation to open collapsed alveoli and improve oxygenation. No studies have assessed the effect of recruitment maneuvers on oxygenation in patients with severe ARDS due to COVID-19. However, a systematic review and meta-analysis of 6 trials of recruitment maneuvers in patients with ARDS who did not have COVID-19 found that recruitment maneuvers reduced mortality, improved oxygenation 24 hours after the maneuver, and decreased the need for rescue therapy.[30] Because recruitment maneuvers can cause barotrauma or hypotension, patients should be closely monitored during recruitment maneuvers. If a patient decompensates during recruitment maneuvers, the maneuver should be stopped immediately.

The importance of properly performing recruitment maneuvers was illustrated by an analysis of 8 randomized controlled trials in patients without COVID-19 (n = 2,544) that found that recruitment maneuvers did not reduce hospital mortality (risk ratio 0.90; 95% CI, 0.78–1.04).[22] However, a subgroup analysis found that traditional recruitment maneuvers significantly reduced hospital mortality (risk ratio 0.85; 95% CI, 0.75–0.97). Mortality was higher among patients who were treated with incremental PEEP titration recruitment maneuvers than among those who were treated with traditional recruitment maneuvers, but this difference was not statistically significant (risk ratio 1.06; 95% CI, 0.97–1.17).

Although there are no published studies on the use of inhaled nitric oxide in patients with COVID-19, a Cochrane review of 13 trials evaluated the use of inhaled nitric oxide in patients with ARDS and found that it did not reduce mortality.[31] Because the review showed a transient benefit for oxygenation, it is reasonable to attempt using inhaled nitric oxide as a rescue therapy in patients with COVID-19 and severe ARDS after other options have failed. However, if the use of nitric oxide does not improve a patient's oxygenation, it should be tapered quickly to avoid rebound pulmonary vasoconstriction, which may occur when nitric oxide is discontinued after prolonged use.

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Pharmacologic Interventions for Critically Ill Patients

Last Updated: May 31, 2022

Empiric Broad-Spectrum Antibiotic Therapy

Recommendations

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

Rationale

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

There are no clinical trials that have evaluated the use of empiric broad-spectrum antibiotics in patients with severe or critical COVID-19 or other coronavirus infections. Routine, empiric use of antibiotics in patients with severe or critical COVID-19 **is not recommended (BIII)**; this recommendation is intended to mitigate the unintended consequences of side effects and resistance. The use of antibiotics may be considered in specific situations, such as the presence of a lobar infiltrate on a chest X-ray, leukocytosis, an elevated serum lactate level, microbiologic data, or shock.

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

Therapeutic Management of Hospitalized Adults With COVID-19

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

Immune-Based Therapy

See Immunomodulators for recommendations on the use of immunomodulators.

Adjunctive Therapy

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

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Extracorporeal Membrane Oxygenation for Adults

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Recommendation

- There is insufficient evidence for the COVID-19 Treatment Guidelines Panel to recommend either for or against the use of extracorporeal membrane oxygenation (ECMO) in adults with COVID-19 and refractory hypoxemia.

Rationale

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

The clinical outcomes for patients with ARDS who are treated with ECMO are variable and depend on multiple factors, including the etiology of hypoxemic respiratory failure, the severity of pulmonary and extrapulmonary illness, the presence of comorbidities, and the ECMO experience of the individual center.[5-7] Several multicenter, observational cohort studies from the first half of 2020[8-10] reported that patients who required ECMO for COVID-19 had a similar mortality to patients in a 2018 randomized study who did not have COVID-19 but who had ARDS and received ECMO.[3]

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

Without data from controlled trials that have evaluated the use of ECMO in patients with COVID-19 and hypoxemic respiratory failure (e.g., ARDS), the benefits of ECMO cannot be clearly defined for this patient population.

Clinicians who are interested in using ECMO should try to enter their patients into clinical trials or clinical registries so that more informative data can be obtained. More information on the use of ECMO in patients with COVID-19 can be found on ELSO's Extracorporeal Membrane Oxygenation in COVID-19 website and ClinicalTrials.gov.

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Introduction to Critical Care Management of Children With COVID-19

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

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

Selected Clinical Manifestations of COVID-19 Critical Illness

Inflammatory Response

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

Multisystem Inflammatory Syndrome in Children

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

Cardiac Dysfunction, Including Myocarditis

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

Thromboembolic Events

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

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

Acute Kidney Injury

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

Neurologic Involvement

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

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

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

Sedation Management

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

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

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

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

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

Post-Intensive Care Syndrome

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

Acknowledgments

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

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Hemodynamic Considerations for Children

Last Updated: May 31, 2022

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

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

Recommendation

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

Rationale

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

Recommendation

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

Rationale

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

However, given the spectrum of hemodynamic perturbations observed and because approximately a third of children with MIS-C exhibit left ventricular dysfunction, cardiac ultrasonography may have particular value in MIS-C.[4]

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

Recommendation

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

Rationale

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

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

Recommendations

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

Rationale

Use of vasoactive infusions should be considered for children with shock due to COVID-19 if signs of

shock persist after resuscitation with 40 mL/kg to 60 mL/kg of fluid, or sooner if there is evidence of cardiac dysfunction or signs of fluid overload (e.g., tachypnea, hepatomegaly). Similar principles may be applied to patients with MIS-C, particularly because their clinical presentation overlaps significantly with the clinical presentation of children with septic shock due to other causes. However, given the high prevalence of cardiac dysfunction in patients with MIS-C, clinicians should consider performing echocardiography or cardiac ultrasound early in the initial resuscitation if MIS-C is suspected and consider initiating a vasoactive infusion if cardiac dysfunction is identified.

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

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

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

Recommendation

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

Rationale

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

Additional Recommendations

- For the acute resuscitation of children with COVID-19 or MIS-C and shock, the Panel recommends the use of **crystalloids** rather than albumin **(AIIb)**.
- The Panel **recommends against** using **hydroxyethyl starches** for intravascular volume replacement in children with COVID-19 or MIS-C and sepsis or septic shock **(AIII)**.

- For children with refractory shock who have recently completed a course of corticosteroids to treat COVID-19, the Panel recommends using low-dose corticosteroid therapy ("shock-reversal") over no corticosteroid therapy **(CIII)**.
  - Children who are currently receiving corticosteroids for COVID-19 or MIS-C are generally receiving sufficient glucocorticoid replacement therapy and do not require additional hydrocortisone for refractory shock.

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Oxygenation and Ventilation for Children

Last Updated: September 26, 2022

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

Goal of Oxygenation

Recommendations

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

Rationale

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

The limitations of currently available measurement devices should be considered when using pulse oximetry to manage children with COVID-19 or PARDS. Observational studies in children have reported that pulse oximetry may be inaccurate, particularly at lower oxygen saturations (≤90%) and for children who are Black.[4,5] These reports are consistent with several adult observational studies that also identified inaccuracies in pulse oximetry measurements, particularly for patients with darker skin pigmentation.[6-8] See Clinical Spectrum of SARS-CoV-2 Infection for more information.

Although procedures vary across institutions, the treatment of most children with PARDS who are critically ill is managed without the use of arterial lines or arterial blood gas testing, because arterial line placement in children, especially young children, can result in complications.[9-11] Clinicians should monitor for adequate delivery of oxygen or consider lowering the threshold for arterial line placement if a patient's SpO_2 measurements could be unreliable (e.g., for children who have darker skin or low SpO_2 levels). Monitoring methods could include observing the patient for altered mentation, measuring venous oxygen saturation, or using near-infrared spectroscopy.

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

Recommendation

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

Rationale

No high-quality studies have evaluated the use of HFNC oxygen or NIV in children with COVID-19. Therefore, when choosing a mode of respiratory support for children with COVID-19, the principles of management used for patients without COVID-19 should be followed. Both the *Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children* and PALICC recommend the use of NIV for children with respiratory failure who have no indication for intubation.[12,13]

Furthermore, the response to NIV, particularly for children with more severe hypoxemia or high work of breathing, should be gauged early (within the first several hours). If the patient does not show improvement, intubation should be considered. To unload respiratory muscles, bilevel modes of NIV (with inspiratory pressure augmentation, such as BiPAP), if tolerated, are preferred over the use of continuous positive airway pressure (CPAP) alone, although CPAP is an alternative for children who cannot achieve an adequate seal with the NIV interface or who have significant patient-ventilator asynchrony.[12]

HFNC oxygen is a relatively new, but increasingly used, mode of respiratory support for infants and children with acute respiratory failure.[14] Data from studies evaluating the effectiveness of HFNC oxygen relative to NIV or conventional oxygen are limited to studies of children with pneumonia in limited-resource settings and studies of children with bronchiolitis. Two randomized controlled trials of children with pneumonia were conducted in limited-resource settings. One study demonstrated a slightly lower relative risk of mortality with the use of HFNC oxygen when compared with conventional oxygen therapy (aHR 0.79; 95% CI, 0.54–1.16), although the results were not statistically significant.[15] The other trial demonstrated that children treated with bubble CPAP ventilation had a lower risk of mortality than children who received low-flow oxygen (relative risk 0.25; 95% CI, 0.07–0.89; $P = 0.02$).[16] The results also indicated that for the composite outcome of treatment failure, there was no difference between the use of HFNC oxygen and bubble CPAP (relative risk 0.50; 99.7% CI, 0.11–2.29).

A randomized, noninferiority trial compared HFNC oxygen (2 L/kg/min) and nasal CPAP among 142 infants aged <6 months with bronchiolitis not caused by COVID-19.[17] The primary outcome was treatment failure within 24 hours, defined as an increase of ≥1 point in the modified Wood's Clinical Asthma Score (M-WCAS) or Échelle Douleur Inconfort Nouveau-Né (EDIN) score (a neonatal pain and discomfort scale), a respiratory rate >60 breaths/min and an increase of >10 breaths/min from baseline, or >2 severe apnea episodes per hour. Treatment failure occurred more often in the HFNC oxygen arm than in the nasal CPAP arm (51% vs. 31%), a result that failed to meet the prespecified noninferiority margin. Notably, in the HFNC oxygen arm, 72% of the patients who had treatment failure were managed successfully with nasal CPAP, and there were no differences between the arms for intubation rates or length of stay in the pediatric intensive care unit (PICU).

A systematic review of the noninferiority trial and 2 smaller trials comparing HFNC oxygen to nasal CPAP summarized the results of 213 infants and children aged ≤2 years with bronchiolitis.[18] Treatment failure

in the 2 smaller trials was rare, and no differences were detected between the HFNC oxygen and nasal CPAP arms for any of the clinical outcomes.[19,20]

In a study that assessed whether higher flow rates of HFNC oxygen improved outcomes, 286 infants aged ≤6 months and with severe bronchiolitis were randomized to receive HFNC oxygen 2 L/kg/min or HFNC oxygen 3 L/kg/min.[21] The primary outcome of treatment failure (i.e., an increase of ≥1 point in M-WCAS or EDIN score, a respiratory rate >60 breaths/min and an increase of >10 breaths/min from baseline, or >2 severe apnea episodes per hour) occurred in 38.7% of the infants in the 2 L/kg/min arm and in 38.9% of the infants in the 3 L/kg/min arm ($P = 0.98$). Patient discomfort, as measured by EDIN score, occurred more often in the 3 L/kg/min arm than in the 2 L/kg/min arm (43% vs. 16%; $P = 0.002$).

HFNC oxygen is increasingly being used in children. These studies highlight the potential role of an HFNC oxygen trial in the management of children with acute respiratory failure due to COVID-19, particularly for infants and young children who may have NIV-related challenges, such as poor mask fit, discomfort, or patient-ventilator asynchrony. For the use of HFNC oxygen in children, consider flow rates of up to 2 L/kg/min, with a maximum of 60 L/min. If patients do not improve within the first few hours of receiving HFNC oxygen, their treatment should be escalated to NIV or intubation.

Awake Prone Positioning for Children Not Receiving Mechanical Ventilation

Recommendations

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

Rationale

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

Intubation for Mechanical Ventilation in Children With Acute COVID-19

Recommendations

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

Rationale

To optimize the safety of patients and health care workers and maximize first-attempt success, intubation should be performed in a controlled setting by an experienced practitioner. In addition, cuffed endotracheal tubes are preferred for children of all ages to minimize leaks around the endotracheal tube,

ensure delivery of ventilator pressure, decrease the risk of aspiration, reduce the need for endotracheal tube exchange, and reduce aerosolization of respiratory secretions during mechanical ventilation.[3,22-24]

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

Recommendations

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

- The Panel recommends using low tidal volume (VT) ventilation (VT 4–8 mL/kg of predicted body weight) over higher VT ventilation (VT >8 mL/kg) **(AIIb)**.
- The Panel recommends targeting plateau pressures of ≤28 cm H_2O for children with normal chest wall compliance and ≤32 cm H_2O for those with impaired chest wall compliance **(AIII)**.
- The Panel recommends using a higher positive end-expiratory pressure (PEEP) strategy (i.e., 10–15 cm H_2O or higher in patients with severe PARDS) over a lower PEEP strategy, titrated based on observed responses in oxygenation, hemodynamics, and respiratory system compliance **(BIIb)**.
- The Panel recommends permissive hypercapnia (e.g., pH 7.15–7.30), if needed, to remain within lung-protective strategies and to minimize ventilator-associated lung injury, provided the patient does not have a coexisting condition that would be worsened by acidosis (e.g., severe pulmonary hypertension, ventricular dysfunction, intracranial hypertension) **(AIII)**.
- The Panel **recommends against** the routine use of **inhaled nitric oxide (AIII)**.

Rationale

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

A large observational study conducted in 71 international PICUs reported that for patients with mild to moderate acute respiratory distress syndrome (ARDS), less adherence to the recommended VT of 5 mL/kg to 8 mL/kg (or 3 mL/kg to 6 mL/kg for patients with severe ARDS) was associated with higher mortality and with more time on ventilation.[25] In general, supraphysiologic VT ventilation (>8 mL/kg) should not be used in patients with PARDS, and VT should be adjusted within the acceptable range to maintain other lung-protective ventilation targets (e.g., maintaining ≤28 cm H_2O plateau pressure). The use of ultra-low VT ventilation (<4 mL/kg) has not been systematically studied in children, so it should be used with caution.

The ARDS Network established a ventilator protocol that includes suggested low PEEP/high FiO_2 levels.[26] The protocol suggests that for patients receiving FiO_2 ≥0.6, a PEEP level of ≥10 cm H_2O would be implemented, which aligns with recommendations from PALICC. Two observational studies have reported better clinical outcomes associated with use of the suggested (or higher) PEEP levels compared to lower PEEP levels.[25,27] The multicenter studies, which included nearly 1,500 pediatric patients with ARDS, demonstrated that PEEP levels lower than those recommended by the ARDS Network were associated with higher mortality.

Inhaled nitric oxide can be considered as a rescue therapy for children with severe PARDS and COVID-19. In a small, randomized trial, the use of inhaled nitric oxide resulted in reduced use of

extracorporeal membrane oxygenation (ECMO).[28] However, inhaled nitric oxide has a heterogeneous treatment effect, and many patients do not show improved gas exchange. Although adverse effects are rare, use of inhaled nitric oxide can have a substantial effect on health care costs. Therefore, inhaled nitric oxide should not be considered routine therapy for children with PARDS or COVID-19 who are receiving mechanical ventilation.

Fluid Management for Children With PARDS

Recommendation

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

Rationale

There is no evidence that fluid management in children with PARDS due to COVID-19 should differ from fluid management in patients with PARDS due to other causes. Therefore, the Panel's recommendation aligns with the PALICC recommendation.[1] No pediatric randomized trials have directly compared a liberal fluid strategy to a conservative fluid strategy in patients with PARDS of any etiology. Several observational studies have demonstrated an association between greater fluid overload and worse clinical outcomes, including fewer ventilator-free days and increased mortality.[29-31]

In a multicenter study of 168 children with acute lung injury, daily and cumulative fluid balance were measured over the first 7 days after participants met the inclusion criteria. After adjusting for demographic characteristics, pediatric risk of mortality III (PRISM III) scores, vasopressor use, and the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen, an increasing cumulative fluid balance on Day 3 was associated with fewer ventilator-free days, but no association with mortality was detected.[29]

A more recent single-center study that included 732 children with acute lung injury demonstrated an association between higher cumulative fluid balance on Days 5 to 7 and increased mortality (for 100 mL/kg on Day 5, OR 1.34; 95% CI, 1.11–1.61) after adjusting for oxygenation index, the number of nonpulmonary organ failures, immunocompromised status, and vasopressor scores. Also, greater cumulative fluid balance on Days 4 to 7 was associated with a lower probability of successful extubation by Day 28.[31] Collectively, the findings from these pediatric observational studies demonstrate the potential harm of fluid overload in children with PARDS, particularly after 3 to 4 days of illness.

These results are consistent with the findings from FACTT, a trial of conservative versus liberal fluid management strategies in adults.[32] In adults, FACTT found no difference between the arms for 60-day mortality, but the conservative strategy arm demonstrated improved oxygenation and less time on mechanical ventilation and in the intensive care unit when compared with the liberal strategy arm. However, no analysis of data from prospective pediatric trials delineates a causal relationship between a specific, protocolized fluid management strategy, or the timing of such a strategy, and clinical outcomes. Therefore, an individualized fluid management approach that is titrated to maintain intravascular volume while preventing excessive positive fluid balance, as suggested by the 2015 PALICC recommendation, is appropriate.[1]

Neuromuscular Blockade for Mechanically Ventilated Children With Severe PARDS

Recommendation

- For mechanically ventilated children with severe PARDS and COVID-19, the Panel recommends

minimal yet effective use of neuromuscular blocking agents in conjunction with sedation, if sedation alone is inadequate to achieve lung-protective ventilation **(BIII)**.

Rationale

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

Therapies for Mechanically Ventilated Children With Severe PARDS and Refractory Hypoxemia

Recommendations

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

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

Rationale

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

One randomized controlled trial and 2 propensity-matched, observational studies have evaluated the use of inhaled nitric oxide in patients with PARDS since the publication of the PALICC recommendations. The randomized controlled trial included 55 patients and found that the use of inhaled nitric oxide resulted in no statistical difference between the arms for 28-day mortality (8% mortality in the inhaled nitric oxide arm vs. 28% in the placebo arm), although the trial was underpowered for this outcome.[28] However, the inhaled nitric oxide arm had approximately 5 more ventilator-free days than the placebo arm, a result that was primarily mediated by avoiding the use of ECMO. These results have been corroborated by observational studies, which also reported more ventilator-free days for patients who received inhaled nitric oxide.[33,34] Although the evidence is insufficient to recommend the use of inhaled nitric oxide for all patients with ARDS, in cases of severe hypoxemia, it can be considered as a rescue therapy to potentially avoid the use of ECMO.

No new studies have evaluated the role of prone positioning in PARDS, although a large, multicenter trial is ongoing. Therefore, the Panel's recommendation to consider prone positioning in cases of severe PARDS aligns with the PALICC recommendation and is supported by adult data, primarily from PROSEVA, a trial on prone positioning in patients with ARDS.[35]

The 2015 PALICC recommendations included the use of careful recruitment maneuvers with incremental and decremental adjustments in PEEP.[1] In children, this approach to recruitment maneuvers is preferred over sustained inflation maneuvers due to the increased risk of harm from barotrauma and hemodynamic compromise in patients with sustained inflation. Clinical trials in adults have highlighted the potential harm of applying recruitment maneuvers to patients who may not have recruitable lung.[36,37] Therefore, although there is insufficient evidence to recommend either for or against the use of recruitment maneuvers in children with refractory hypoxemia, if recruitment maneuvers are used, the preferred strategy is slow, incremental and decremental adjustments in PEEP.

Since the publication of the 2015 PALICC recommendations, 2 small randomized controlled trials have examined the use of HFOV for PARDS.[38,39] Neither study found a significant difference for mortality. Several observational studies using propensity matching have shown either no difference in outcomes between the HFOV and conventional ventilation arms or a potential for higher mortality or a longer ventilation time with the use of HFOV when compared with conventional ventilation.[40-44] In some of these analyses, residual confounding has been a concern. A large, multicenter randomized controlled trial of HFOV for PARDS is ongoing. Therefore, the Panel has determined that there is insufficient evidence to recommend either for or against the use of HFOV in COVID-19-related PARDS. Some concerns have been raised about the use of HFOV and the aerosolization of COVID-19; however, adding a filter to the expiratory limb of the HFOV circuit may alleviate these concerns.

Multisystem Inflammatory Syndrome in Children

More than half of the patients with multisystem inflammatory syndrome in children (MIS-C) require mechanical ventilation or NIV.[45-47] For patients with MIS-C, the indications for mechanical ventilation vary and include shock or cardiac dysfunction, pulmonary edema, procedural preparation (e.g., to facilitate sedation for central venous catheter placement), respiratory failure, or neurologic failure. The management of oxygenation and ventilation in children with MIS-C should follow the usual principles of shock management outlined in the Surviving Sepsis Campaign guidelines for children, as well as the principles for clinical management of heart failure and general critical care, as appropriate.[13]

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Extracorporeal Membrane Oxygenation for Children

Last Updated: May 31, 2022

Recommendation

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

Rationale

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

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

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

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

Pediatric clinicians should consider entering patients into clinical trials or registries to inform future

recommendations regarding use of ECMO in children with COVID-19. The following resources provide more information on an international ECMO registry and on clinical trials evaluating ECMO in children with COVID-19:

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

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Antiviral Agents, Including Antibody Products

Last Updated: December 28, 2022

Remdesivir is the only antiviral drug that is approved by the Food and Drug Administration (FDA) for the treatment of COVID-19. Ritonavir-boosted nirmatrelvir (Paxlovid), molnupiravir, and high-titer COVID-19 convalescent plasma (CCP) have received Emergency Use Authorizations (EUAs) from the FDA for the treatment of COVID-19. Tixagevimab 300 mg plus cilgavimab 300 mg (Evusheld) has received an EUA that allows these anti-SARS-CoV-2 monoclonal antibodies to be used as SARS-CoV-2 pre-exposure prophylaxis (PrEP) in certain patients.

Summary Recommendations

Recommendations for Treating Nonhospitalized Adults

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends the following anti-SARS-CoV-2 therapies as preferred treatments for COVID-19. These drugs are listed in order of preference:
  - **Ritonavir-boosted nirmatrelvir (Paxlovid) (AIIa**)
  - **Remdesivir (BIIa)**
- The Panel recommends **molnupiravir** as an alternative therapy when neither of the preferred therapies are available, feasible to use, or clinically appropriate **(CIIa)**.

Recommendations for Treating Nonhospitalized Children

- For recommendations on using antiviral therapy in nonhospitalized children, see Therapeutic Management of Nonhospitalized Children With COVID-19.

Recommendations for Treating Hospitalized Adults or Children

- See Therapeutic Management of Hospitalized Adults With COVID-19 and Therapeutic Management of Hospitalized Children With COVID-19 for recommendations on using remdesivir with or without immunomodulators in certain hospitalized patients.

Antiviral Treatments With Insufficient Evidence

- There is insufficient evidence for the Panel to recommend either for or against the use of high-titer CCP for the treatment of COVID-19 in hospitalized or nonhospitalized patients who are immunocompromised.
  - Some Panel members would use CCP to treat an immunocompromised patient with significant symptoms attributable to COVID-19 and with signs of active SARS-CoV-2 replication and who is having an inadequate response to available therapies. In these cases, clinicians should attempt to obtain high-titer CCP from a vaccinated donor who recently recovered from COVID-19 likely caused by a SARS-CoV-2 variant similar to the variant causing the patient's illness.
- There is insufficient evidence for the Panel to recommend either for or against the use of high-titer CCP for the treatment of COVID-19 in nonhospitalized patients who are immunocompetent.

Antiviral Treatments That the Panel Recommends Against

- The Panel **recommends against** the use of the following drugs for the treatment of COVID-19, except in a clinical trial:
  - **Interferons** in nonhospitalized patients **(AIIa)**
  - **Interferon alfa** or **lambda** in hospitalized patients **(AIIa)**
  - **Nitazoxanide (BIIa)**
- The Panel **recommends against** the use of the following drugs for the treatment of COVID-19:
  - **Bamlanivimab plus etesevimab, bebtelovimab, casirivimab plus imdevimab,** or **sotrovimab (AIII)**
  - **Chloroquine** or **hydroxychloroquine** and/or **azithromycin** in hospitalized **(AI)** and nonhospitalized patients **(AIIa)**
  - **CCP** in hospitalized patients who are immunocompetent **(AI)**
  - **Lopinavir/ritonavir** and **other HIV protease inhibitors** in hospitalized **(AI)** and nonhospitalized patients **(AIII)**

Summary Recommendations, continued

- **Systemic interferon beta** in hospitalized patients **(AI)**

Pre-Exposure Prophylaxis for SARS-CoV-2 Infection

- Tixagevimab plus cilgavimab is authorized by the FDA for use as SARS-CoV-2 PrEP in people who are not expected to mount an adequate immune response to COVID-19 vaccination or those with contraindications for COVID-19 vaccines.
- The prevalence of Omicron subvariants that are resistant to tixagevimab plus cilgavimab is rapidly increasing in all regions of the United States.
- The decision to administer tixagevimab plus cilgavimab should be based on the regional prevalence of the resistant subvariants, the individual patient's risks, the available resources, and logistics.
- Individuals who receive tixagevimab plus cilgavimab as PrEP should continue to take precautions to avoid infection. If they experience signs and symptoms consistent with COVID-19, they should be tested for SARS-CoV-2 and, if infected, promptly seek medical attention.
- In the absence of an alternative option for PrEP, the Panel recommends the use of **tixagevimab 300 mg plus cilgavimab 300 mg** as PrEP for eligible individuals **(BIIb)**. See Prevention of SARS-CoV-2 Infection for more information.

The sections on Chloroquine or Hydroxychloroquine and/or Azithromycin, Lopinavir/Ritonavir and Other HIV Protease Inhibitors, and Nitazoxanide have been archived. The Panel will no longer be updating the information on these therapies.

Each recommendation in the Guidelines receives 2 ratings that reflect the strength of the recommendation and the quality of the evidence that supports it. See Guidelines Development for more information.

Remdesivir

Last Updated: December 1, 2022

Remdesivir is a nucleotide prodrug of an adenosine analog. It binds to the viral RNA-dependent RNA polymerase and inhibits viral replication by terminating RNA transcription prematurely. Remdesivir has demonstrated in vitro and in vivo activity against SARS-CoV-2.[1] Remdesivir retains in vitro neutralization activity against the Omicron variant and its subvariants.[2-5]

Intravenous remdesivir is approved by the Food and Drug Administration (FDA) for the treatment of COVID-19 in adults and pediatric patients aged ≥28 days and weighing ≥3 kg. In nonhospitalized patients with mild to moderate COVID-19 who are at high risk of progressing to severe disease, remdesivir should be started within 7 days of symptom onset and administered for 3 days. Hospitalized patients should receive remdesivir for 5 days or until hospital discharge, whichever comes first.[6] See Table 4e for more information.

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 4a for more information.

Recommendations

- For the Panel's recommendations and information on the clinical efficacy of using remdesivir to treat high-risk, nonhospitalized patients with mild to moderate COVID-19, see Therapeutic Management of Nonhospitalized Adults With COVID-19.
- For the Panel's recommendations and information on the clinical efficacy of using remdesivir with or without immunomodulators to treat certain hospitalized patients, see Therapeutic Management of Hospitalized Adults With COVID-19.
- The data on using combinations of antiviral therapies for the treatment of COVID-19 are limited.[7] Clinical trials are needed to determine the role of combination therapy in treating certain patients.

Monitoring, Adverse Effects, and Drug-Drug Interactions

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

Before starting patients on remdesivir, the FDA recommends performing estimated glomerular filtration rate (eGFR), liver function, and prothrombin time tests as clinically appropriate and repeating these tests during treatment as clinically indicated. However, it should be noted that in the PINETREE study, in which outpatients with mild to moderate COVID-19 received remdesivir for 3 days, baseline serum creatinine was not required by the protocol for patients weighing >48 kg.[8] Remdesivir may need to be discontinued if a patient's alanine transaminase (ALT) level increases to >10 times the upper limit of normal, and it should be discontinued if increases in ALT levels and signs or symptoms of liver inflammation are observed.[6]

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

Patients who are severely immunocompromised may have a prolonged duration of SARS-CoV-2 replication, which may lead to rapid viral evolution. There is concern that using a single antiviral agent in these patients may result in the emergence of resistant virus.[9] Additional studies are needed to assess this risk. The role of combination antiviral therapy in the treatment of COVID-19 is not yet known.

Currently, no clinical drug-drug interaction studies of remdesivir have been conducted. In vitro, remdesivir is a minor substrate of cytochrome P450 (CYP) 3A4 and a substrate of the drug transporters organic anion transporting polypeptide (OATP) 1B1 and P-glycoprotein. It is also an inhibitor of CYP3A4, OATP1B1, OATP1B3, and multidrug and toxin extrusion protein (MATE) 1.[6] See Table 4e for more information.

Considerations in Patients With Renal Insufficiency

Each 100-mg vial of remdesivir lyophilized powder contains 3 g of sulfobutylether beta-cyclodextrin sodium (SBECD), and each 100-mg/20-mL vial of remdesivir solution contains 6 g of SBECD.[6] 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.[10] Accumulation of SBECD in patients with renal impairment may result in liver and renal toxicities. Clinicians may consider preferentially using the lyophilized powder formulation (which contains less SBECD) in patients with renal impairment.

Because both remdesivir formulations contain SBECD, patients with an eGFR of <50 mL/min were excluded from some clinical trials of remdesivir; other trials had an eGFR cutoff of <30 mL/min. The FDA product label does not recommend using remdesivir in patients with an eGFR of <30 mL/min due to a lack of data.[11]

The CATCO study was a multicenter, open-label randomized controlled trial that compared the use of remdesivir to standard of care in hospitalized adults with COVID-19.[12] The study did not exclude patients with renal impairment. A post hoc analysis was done for 59 patients with a baseline eGFR of <30 mL/min; 15 of these patients were on dialysis. The median age of the cohort was 74 years. Thirty-four patients received the lyophilized powder formulation of remdesivir for a median duration of 10 days, while 25 patients received standard of care. More men were enrolled in the standard of care arm, and patients in this arm also had a lower median eGFR at baseline (12.4 mL/min) than those in the remdesivir arm (22.7 mL/min).

Clinical laboratory evaluations were performed only on Day 5. There was no increased risk of renal toxicity at Day 5 among the individuals who received remdesivir when compared with those who received standard of care. There were also no statistically significant differences between the arms in the need for new dialysis, the need for new mechanical ventilation, or mortality.

This study has limitations, including a small sample size. However, it provides reassurance regarding the safety of using remdesivir in patients with renal impairment. The results are consistent with a systematic review of observational studies[13] and other retrospective studies that have reported that the use of remdesivir was not associated with an increased incidence of adverse effects in patients with COVID-19 who had baseline eGFRs of <30 mL/min.[14] These data suggest that remdesivir can be used in patients with an eGFR of <30 mL/min if the potential benefits outweigh the risks.

Considerations in Pregnancy

Remdesivir should be offered to pregnant individuals if it is indicated.

While pregnant patients were excluded from the clinical trials that evaluated the safety and efficacy of remdesivir for the treatment of COVID-19, subsequent reports on the use of remdesivir in pregnant patients have been reassuring. Among 86 pregnant and postpartum patients who were hospitalized with severe COVID-19 and who received remdesivir through a compassionate use program, the therapy was well tolerated, with a low rate of serious adverse effects.[15]

Among 95 pregnant patients with moderate, severe, or critical COVID who were included in a secondary analysis of data from a COVID-19 pregnancy registry in Texas, the composite maternal and neonatal outcomes were similar between those who received remdesivir (n = 39) and those who did not.[16] Remdesivir was discontinued in 16.7% of patients due to elevated levels of transaminases. It was not possible to determine whether these elevated levels were secondary to the drug, COVID-19, or pregnancy-related conditions.

The results of the secondary analysis should be interpreted with caution, given that clinicians were more likely to choose to administer remdesivir to pregnant patients with more severe illness. Those who were treated with remdesivir were more likely to have had COVID-19 for a longer duration by the time they were admitted to the hospital. They were also more likely to require oxygen support at admission and to have a longer hospital stay.

A systematic review of 13 observational studies that included 113 pregnant people also reported few adverse effects of remdesivir in pregnant patients with COVID-19. The most common adverse effect was a mild elevation in transaminase levels.[17]

Considerations in Children

Please see Special Considerations in Children, Therapeutic Management of Nonhospitalized Children With COVID-19, and Therapeutic Management of Hospitalized Children With COVID-19.

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Table 4a. Remdesivir: Selected Clinical Data

Last Updated: August 8, 2022

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. Studies of hospitalized patients are listed first, followed by 1 study of nonhospitalized patients.

Methods	Results	Limitations and Interpretation
ACTT-1: Multinational, Double-Blind, Placebo-Controlled Trial of Remdesivir in Hospitalized Patients With COVID-19 in 10 Countries[1]		

Key Inclusion Criteria
• Laboratory-confirmed SARS-CoV-2 infection
• ≥1 of the following:
  • Pulmonary infiltrates
  • SpO_2 ≤94% on room air
  • Need for supplemental oxygen, HFNC oxygen, NIV, MV, or ECMO
Key Exclusion Criteria
• ALT or AST >5 times ULN
• eGFR <30 mL/min
Interventions
• RDV 200 mg IV on Day 1, then RDV 100 mg IV once daily for up to 9 more days (n = 541)
• Placebo for up to 10 days (n = 521)
Primary Endpoint
• Time to clinical recovery
Key Secondary Endpoints
• Clinical status at Day 15, as measured by an OS
• Mortality by Day 29
• Occurrence of SAEs
	Participant Characteristics
	• Mean age 59 years; 64% men; 53% White, 21% Black, 13% Asian, 24% Hispanic/Latinx
	• Coexisting conditions: 26% with 1; 55% with ≥2
	• 13% not on oxygen; 41% on supplemental oxygen; 18% on HFNC oxygen or NIV; 27% on MV or ECMO
	• Median time from symptom onset to randomization: 9 days (IQR 6–12 days)
	• 23% received corticosteroids during study
	Primary Outcomes
	• Time to clinical recovery: 10 days in RDV arm vs. 15 days in placebo arm (rate ratio for recovery 1.29; 95% CI, 1.12–1.49; $P < 0.001$)
	• Benefit of RDV greatest in patients randomized during first 10 days after symptom onset and those who required supplemental oxygenation at enrollment
	• No difference in time to recovery for patients on HFNC oxygen, NIV, MV, or ECMO at enrollment
	Secondary Outcomes
	• Improvement in clinical status at Day 15 more likely in RDV arm (OR 1.5; 95% CI, 1.2–1.9; $P < 0.001$)
	• No difference between arms in mortality by Day 29
	• Occurrence of SAEs: 25% in RDV arm vs. 32% in placebo arm
		Key Limitations
		• Wide range of disease severity among patients; study not powered to detect differences within subgroups
		• Study not powered to detect differences in mortality between arms
		• No data on longer-term morbidity
		Interpretation
		• In patients with severe COVID-19, RDV reduced the time to clinical recovery.
		• The benefit was most apparent in hospitalized patients who were receiving supplemental oxygen.
		• There was no observed benefit in those on HFNC oxygen, NIV, MV, or ECMO, but the study was not powered to detect differences within subgroups.

Methods	Results	Limitations and Interpretation
CATCO: Multicenter, Open-Label, Pragmatic RCT of Remdesivir in Hospitalized Patients With COVID-19 in Canada[2]		

Key Inclusion Criterion
• Laboratory-confirmed SARS-CoV-2 infection
Key Exclusion Criterion
• Already receiving RDV
Interventions
• RDV 200 mg IV on Day 0, then RDV 100 mg IV once daily on Days 1–9 (n = 634)
• Local SOC (n = 647)
Primary Endpoint
• In-hospital mortality
Key Secondary Endpoints
• New need for MV
• Hospital LOS
• Incidence of hepatic dysfunction, incidence of need for dialysis, and change in SCr at Day 5
	Participant Characteristics
	• Median age 66 years; 60% men; 41% White
	• Median time from symptom onset to randomization: 8 days
	• At entry:
	  • 54% on low-flow oxygen
	  • 24% on HFNC oxygen
	  • 9% on MV
	• Rates of comorbidities were similar between arms.
	• 87% in both arms were receiving corticosteroids at baseline
	Primary Outcome
	• In-hospital mortality: 19% in RDV arm vs. 23% in SOC arm (relative risk 0.83; 95% CI, 0.67–1.03)
	Secondary Outcomes
	• New need for MV: 8% in RDV arm vs. 15% in SOC arm (relative risk 0.53; 95% CI, 0.38–0.75)
	• No significant difference between arms in hospital LOS
	• No difference between arms in incidence of new hepatic dysfunction, incidence of need for dialysis, or change in SCr at Day 5
		Key Limitations
		• Open-label study
		• Information on comorbidities was not available for 26% of patients.
		Interpretation
		• RDV did not decrease in-hospital mortality among patients with COVID-19 compared to SOC.
		• Patients who received RDV were less likely to require MV than patients who received SOC.

Methods	Results	Limitations and Interpretation
DisCoVeRy: Open-Label, Adaptive RCT of Remdesivir in Hospitalized Patients With Moderate or Severe COVID-19 in Europe[3]		
Key Inclusion Criteria • Laboratory-confirmed SARS-CoV-2 infection • Illness of any duration • SpO_2 ≤94% on room air or use of supplemental oxygen, HFNC oxygen, NIV, or MV **Key Exclusion Criteria** • ALT or AST >5 times ULN • Severe chronic kidney disease **Interventions** • RDV 200 mg IV on Day 1, then RDV 100 mg IV once daily for up to 9 days (n = 429) • SOC (n = 428) **Primary Endpoint** • Clinical status at Day 15, as measured by an OS **Key Secondary Endpoints** • Mortality by Day 29 • Occurrence of SAEs	**Participant Characteristics** • Median age 64 years; 70% men; 69% White • 74% with ≥1 coexisting condition • 40% received corticosteroids • Median time from symptom onset to randomization: 9 days in both arms • 61% with moderate disease; 39% with severe disease **Primary Outcome** • No difference between arms in clinical status at Day 15 (OR 0.98; 95% CI, 0.77–1.25; *P* = 0.85) • A prespecified subgroup analysis based on duration of symptoms found no significant difference in clinical status between arms. **Secondary Outcomes** • Mortality by Day 29: 8% in RDV arm vs. 9% in SOC arm • Occurrence of SAEs: 33% in RDV arm vs. 31% in SOC arm (*P* = 0.48)	**Key Limitations** • Open-label study • 440 participants in this study also enrolled in the WHO Solidarity trial. **Interpretation** • There was no clinical benefit of RDV in hospitalized patients who were symptomatic for >7 days and who required supplemental oxygen.

Methods	Results	Limitations and Interpretation
WHO Solidarity Trial, Final Report: Multinational, Open-Label, Adaptive RCT in Hospitalized Patients With COVID-19 in 35 Countries[4]		

Key Inclusion Criterion
• Not known to have received any study drug
Interventions
• RDV 200 mg IV on Day 0, then RDV 100 mg IV once daily on Days 1–9 (n = 4,146)
• Local SOC (n = 4,129)
Primary Endpoint
• In-hospital mortality
Key Secondary Endpoint
• Initiation of MV
	Participant Characteristics
	• 46% aged 50–69 years; 22% aged ≥70 years; 63% men
	• Rates of comorbidities were similar between arms
	• At entry:
	  • 71% on supplemental oxygen
	  • 9% on MV
	• 68% received corticosteroids during study; 4.6% received IL-6 inhibitors
	Primary Outcome
	• In-hospital mortality: 14.5% in RDV arm vs. 15.6% in SOC arm (rate ratio 0.91; 95% CI, 0.82–1.02; $P = 0.12$)
	  • On MV: 42.1% vs. 38.6% (rate ratio 1.13; 95% CI, 0.89–1.42; $P = 0.32$)
	  • Not on MV but receiving oxygen: 14.6% vs. 16.3% (rate ratio 0.87; 95% CI, 0.76–0.99; $P = 0.03$)
	  • Not on oxygen initially: 2.9% vs. 3.8% (rate ratio 0.76; 95% CI, 0.46–1.28; $P = 0.30$)
	Secondary Outcome
	• Initiation of MV: 14.1% in RDV arm vs. 15.7% in SOC arm (rate ratio 0.88; 95% CI, 0.77–1.00; $P = 0.04$)
		Key Limitations
		• Open-label study
		• No data on time from symptom onset to enrollment
		• Data analysis did not separate receipt of low-flow and high-flow oxygen
		Interpretation
		• There was no benefit of RDV in patients who were on MV at baseline.
		• Compared to SOC, RDV had a modest but statistically significant effect on reducing the risk of death or progression to MV in hospitalized patients who required oxygen.

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

Key Inclusion Criteria
• Laboratory-confirmed SARS-CoV-2 infection
• Pulmonary infiltrates
• SpO_2 >94% on room air
Key Exclusion Criteria
• ALT or AST >5 times ULN
• CrCl <50 mL/min
Interventions
• RDV 200 mg IV on Day 1, then RDV 100 mg IV once daily for 9 days (n = 193)
• RDV 200 mg IV on Day 1, then RDV 100 mg IV once daily for 4 days (n = 191)
• Local SOC (n = 200)
Primary Endpoint
• Clinical status at Day 11, as measured by an OS
	Participant Characteristics
	• Demographic and baseline disease characteristics were similar across arms.
	• Median age 57 years; 61% men; 58% White
	• 84% required no supplemental oxygen; 15% required low-flow oxygen; 1% required HFNC oxygen or NIV
	• Concomitant medication use in the 10-day RDV, 5-day RDV, and SOC arms:
	  • Steroids: 15%, 17%, 19%
	  • Tocilizumab: 1%, 1%, 5%
	  • HCQ or CQ: 11%, 8%, 45%
	  • LPV/RTV: 6%, 5%, 22%
	  • AZM: 21%, 18%, 31%
	• Median duration of therapy: 6 days in 10-day RDV arm vs. 5 days in 5-day RDV arm
	Primary Outcome
	• Clinical status at Day 11:
	  • Significantly better in 5-day RDV arm than in SOC arm (OR 1.65; 95% CI, 1.09–2.48; $P = 0.02$)
	  • No difference between 10-day RDV arm and SOC arm ($P = 0.18$)
		Key Limitations
		• Open-label design may have affected decisions on concomitant medications (e.g., more patients in SOC arm received AZM, HCQ or CQ, and LPV/RTV) and time of hospital discharge.
		• No data on time to return to activity for discharged patients
		Interpretation
		• Hospitalized patients with moderate COVID-19 who received 5 days of RDV had better clinical status at Day 11 than those who received SOC.
		• There was no difference in clinical status at Day 11 between patients who received 10 days of RDV and those who received SOC.

Methods	Results	Limitations and Interpretation
GS-US-540-5773 Study: Multinational, Open-Label RCT of 10 Days or 5 Days of Remdesivir Compared With Standard of Care in Hospitalized Patients With Severe COVID-19 in Asia, Europe, and the United States[6]		

Key Inclusion Criteria
• Laboratory-confirmed SARS-CoV-2 infection
• Aged ≥12 years
• Pulmonary infiltrates and SpO_2 ≤94% on room air or receipt of supplemental oxygen
Key Exclusion Criteria
• Need for MV or ECMO
• Multiorgan failure
• ALT or AST >5 times ULN
• Estimated CrCl <50 mL/min
Interventions
• RDV 200 mg IV on Day 1, then RDV 100 mg IV once daily for 4 days (n = 200)
• RDV 200 mg IV on Day 1, then RDV 100 mg IV once daily for 9 days (n = 197)
Primary Endpoint
• Clinical status at Day 14, as measured by an OS
	Participant Characteristics
	• Median age: 61 years in 5-day RDV arm vs. 62 years in 10-day RDV arm
	• 60% men in 5-day RDV arm; 68% men in 10-day RDV arm
	• Oxygen requirements at baseline for 5-day RDV arm and 10-day RDV arm:
	  • None: 17%, 11%
	  • Low-flow oxygen: 56%, 54%
	  • HFNC oxygen or NIV: 24%, 30%
	  • MV or ECMO: 2%, 5%
	• Baseline clinical status worse in 10-day arm than in 5-day arm ($P = 0.02$)
	Primary Outcome
	• After adjusting for baseline clinical status:
	  • Proportion with clinical improvement at Day 14: 65% in 5-day RDV arm vs. 54% in 10-day RDV arm ($P = 0.14$)
		Key Limitations
		• Open-label study
		• Lack of placebo arm
		• Baseline imbalances in clinical status of patients in 5-day RDV and 10-day RDV arms
		Interpretation
		• In hospitalized patients with severe COVID-19 who were not receiving MV or ECMO, using RDV for 5 or 10 days had similar clinical benefits.

Methods	Results	Limitations and Interpretation
PINETREE: Double-Blind, Placebo-Controlled Trial of Remdesivir for 3 Days in Nonhospitalized Patients With COVID-19 Who Were at High Risk of Disease Progression in Denmark, Spain, the United Kingdom, and the United States[7]		
Key Inclusion Criteria • Laboratory-confirmed SARS-CoV-2 infection ≤4 days from screening • Aged ≥12 years • ≥1 risk factor for disease progression or aged ≥60 years • Symptom onset ≤7 days from randomization • ≥1 ongoing COVID-19 symptom **Key Exclusion Criteria** • COVID-19 vaccination • Receipt of supplemental oxygen • Previous hospitalization or treatment for COVID-19 **Interventions** • RDV 200 mg IV on Day 1, then RDV 100 mg IV once daily on Days 2 and 3 (n = 279) • Placebo (n = 283) **Primary Endpoints** • COVID-19-related hospitalization or death from any cause by Day 28 • Occurrence of AEs **Key Secondary Endpoint** • COVID-19-related, medically attended visit or death from any cause by Day 28	**Participant Characteristics** • Mean age 50 years; 30% aged ≥60 years; 52% men; 80% White, 8% Black • 62% with DM; 55% with obesity; 48% with HTN • Median duration of symptoms before first infusion: 5 days (IQR 3–6 days) • Median time from RT-PCR confirmation: 2 days (IQR 1–4 days) **Primary Outcomes** • COVID-19-related hospitalization or death from any cause by Day 28: 2 (0.7%) in RDV arm vs. 15 (5.3%) in placebo arm (HR 0.13; 95% CI, 0.03–0.59; $P = 0.008$) • Occurrence of AEs: 42% in RDV arm vs. 46% in placebo arm **Secondary Outcome** • COVID-19-related, medically attended visit or death from any cause by Day 28: 4 (1.6%) in RDV arm vs. 21 (8.3%) in placebo arm (HR 0.19; 95% CI, 0.07–0.56)	**Key Limitations** • Study halted early due to administrative issues. • Vaccinated individuals were excluded. **Interpretation** • 3 consecutive days of IV RDV resulted in an 87% relative reduction in the risk of hospitalization or death when compared to placebo.

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

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Ritonavir-Boosted Nirmatrelvir (Paxlovid)

Last Updated: December 1, 2022

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

Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using **nirmatrelvir 300 mg with ritonavir 100 mg (Paxlovid)** orally (PO) twice daily for 5 days in nonhospitalized adults **(AIIa)** and pediatric patients aged ≥12 years and weighing ≥40 kg **(BIII)** with mild to moderate COVID-19 who are at high risk of disease progression. Treatment should be initiated as soon as possible and within 5 days of symptom onset. For information on medical conditions that confer high risk, see the Centers for Disease Control and Prevention webpage People With Certain Medical Conditions.
- For recommendations on using ritonavir-boosted nirmatrelvir in nonhospitalized children with COVID-19, see Therapeutic Management of Nonhospitalized Children With COVID-19.
- Ritonavir-boosted nirmatrelvir may be used in patients who are hospitalized for a diagnosis other than COVID-19, provided they have mild to moderate COVID-19, are at high risk of progressing to severe disease, and are within 5 days of symptom onset.

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

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

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

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

Rationale

The EPIC-HR trial enrolled nonhospitalized adults with mild to moderate COVID-19 who were not vaccinated and who were at high risk of progressing to severe disease. The trial demonstrated that starting ritonavir-boosted nirmatrelvir within 5 days of symptom onset in these patients reduced the risk of hospitalization or death through Day 28 by 89% compared to placebo.[3,4] This efficacy is comparable to remdesivir (87% relative reduction)[5] and greater than the efficacy reported for molnupiravir (31% relative reduction).[6] However, these agents have not been directly compared in clinical trials.

Although ritonavir-boosted nirmatrelvir demonstrated a clinical benefit during the EPIC-HR trial, the benefits in unvaccinated people who are at low risk of progression to severe disease or in vaccinated people who are at high risk of progression to severe disease are unclear. The EPIC-SR trial, which included both of these populations, found that ritonavir-boosted nirmatrelvir did not reduce the duration of symptoms and did not have a statistically significant effect on the risk of hospitalization or death compared to placebo, although the event rates were low.[7] Some observational studies evaluated the effect of ritonavir-boosted nirmatrelvir in vaccinated individuals who were at high risk of progression to severe COVID-19, but because of the limitations of observational studies, these data are not definitive.[8-10] For information on treatment considerations for vaccinated individuals, see Therapeutic Management of Nonhospitalized Adults With COVID-19.

Because of the potential for significant drug-drug interactions with concomitant medications, this regimen may not be the optimal choice for all patients. See Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications for more information.

Ritonavir-boosted nirmatrelvir is expected to be active against the Omicron variant and its subvariants,[11] although there is currently a lack of data on the clinical efficacy of ritonavir-boosted nirmatrelvir against these variants.[12-14]

Viral Rebound and Symptom Recurrence

Observational studies and results from the EPIC-HR trial have described SARS-CoV-2 viral rebound and the recurrence of COVID-19 symptoms in some patients who have completed treatment with ritonavir-boosted nirmatrelvir.[15-18] The frequency, mechanism, and clinical implications of these events are unclear. Viral rebound and the recurrence of COVID-19 symptoms can also occur in the absence of treatment with ritonavir-boosted nirmatrelvir.[19,20]

The EPIC-HR trial demonstrated a clinical benefit of ritonavir-boosted nirmatrelvir in patients who were not vaccinated and who were at high risk of progressing to severe COVID-19. To date, the recurrence of COVID-19 symptoms following the use of ritonavir-boosted nirmatrelvir has not been associated with progression to severe COVID-19. Therefore, concerns about the recurrence of symptoms should not be a reason to avoid using ritonavir-boosted nirmatrelvir.[19,21,22]

Longer treatment courses of ritonavir-boosted nirmatrelvir are not authorized by the current EUA, and there are insufficient data on the efficacy of administering a second course.

SARS-CoV-2 Resistance

Viral mutations that lead to substantial resistance to nirmatrelvir have been selected for in vitro studies; the fitness of these mutations is unclear. Surveillance for the emergence of significant resistance to nirmatrelvir is critical.

Severely immunocompromised patients can experience prolonged periods of SARS-CoV-2 replication, which may lead to rapid viral evolution. There are theoretical concerns that using a single antiviral agent in these patients may produce antiviral-resistant viruses. Additional studies are needed to assess this risk. The role of combination antiviral therapy or a longer treatment duration in treating patients who are severely immunocompromised is not yet known.

Additional Considerations

- Nirmatrelvir must be administered with ritonavir to achieve sufficient therapeutic plasma concentrations.
- Patients should complete the 5-day treatment course of ritonavir-boosted nirmatrelvir, because there are concerns that a shorter treatment course may be less effective or lead to resistance.
- If a patient requires hospitalization after starting treatment, the full 5-day treatment course of ritonavir-boosted nirmatrelvir should be completed unless there are drug-drug interactions that preclude its use.
- There are no data on combining ritonavir-boosted nirmatrelvir with other antiviral therapies to treat nonhospitalized patients with COVID-19. Clinical trials are needed to determine whether combination therapy has a role in the treatment of COVID-19.
- The EUA advises against crushing nirmatrelvir and ritonavir tablets. However, some data indicate that the tablets can be split or crushed if necessary.[23]

Monitoring and Adverse Effects

The most common adverse effects of ritonavir-boosted nirmatrelvir are dysgeusia, diarrhea, hypertension, and myalgia. Anaphylaxis and other hypersensitivity reactions have also been reported.

Renal impairment reduces the clearance of nirmatrelvir. In patients with suspected renal impairment, clinicians may consider checking the patient's renal function to inform the dosing of ritonavir-boosted nirmatrelvir. The dose should be reduced to nirmatrelvir 150 mg with ritonavir 100 mg twice daily in patients with moderate renal impairment (i.e., those with an estimated glomerular filtration rate [eGFR] of ≥30 to <60 mL/min).

The EUA states that ritonavir-boosted nirmatrelvir is not recommended for patients with an eGFR of <30 mL/min until more data are available to establish appropriate dosing.[3] Additional information is available in the initial FDA Center for Drug Evaluation and Research review for the EUA of ritonavir-boosted nirmatrelvir.[15] Clinical experience on the use of ritonavir-boosted nirmatrelvir in patients who require hemodialysis is limited.[24] Based on limited data, some groups have proposed dosing adjustments for ritonavir-boosted nirmatrelvir in patients with an eGFR of <30 mL/min and those who require hemodialysis.[25-27] A clinical trial (ClinicalTrials.gov Identifier NCT05487040) that will evaluate the use of ritonavir-boosted nirmatrelvir in patients with COVID-19 and severe renal impairment is currently underway.

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

Drug-Drug Interactions

Ritonavir-boosted nirmatrelvir has significant drug-drug interactions, primarily due to the ritonavir component of the combination. Boosting with ritonavir, which is a strong CYP3A inhibitor and a

P-glycoprotein inhibitor, is required to increase the exposure of nirmatrelvir to a concentration that is effective against SARS-CoV-2. However, it may also increase concentrations of certain concomitant medications, thereby increasing the potential for serious and sometimes life-threatening drug toxicities. Additionally, ritonavir is an inhibitor, inducer, and substrate of various other drug-metabolizing enzymes and/or drug transporters.

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

The treatment course of ritonavir-boosted nirmatrelvir for COVID-19 is 5 days. CYP3A4 inhibition occurs rapidly after initiating ritonavir, with maximum inhibition occurring within 48 hours.[28] After ritonavir is discontinued, 70% to 90% of CYP3A4 inhibition resolves within 2 to 3 days.[29] The time to resolution of inhibition varies based on factors such as the patient's age; therefore, resolution may take longer in some individuals, such as in adults of advanced age. When ritonavir is used for 5 days, its induction properties are less likely to be clinically relevant than when the drug is used chronically (e.g., in people who take HIV protease inhibitors).[30]

Both nirmatrelvir and ritonavir are substrates of CYP3A. Thus, ritonavir-boosted nirmatrelvir should not be given within 2 weeks of administering a strong CYP3A4 inducer (e.g., St. John's wort, rifampin). Ritonavir-boosted nirmatrelvir is **contraindicated** in this setting, as the delayed offset of enzyme induction can reduce the concentrations of nirmatrelvir and ritonavir, which may render the treatment ineffective against SARS-CoV-2. An alternative treatment for COVID-19 should be prescribed instead.

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

Considerations in Pregnancy

Pregnancy is a risk factor for severe COVID-19.[31] However, like many clinical trials of treatments for COVID-19, the EPIC-HR trial excluded pregnant and lactating individuals. Ritonavir has been used extensively during pregnancy in people with HIV and has a favorable safety profile during pregnancy. The mechanisms of action for both nirmatrelvir and ritonavir and the results of animal studies of ritonavir-boosted nirmatrelvir suggest that this regimen can be used safely in pregnant individuals.

Ritonavir-boosted nirmatrelvir should be offered to pregnant and recently pregnant patients with COVID-19 who qualify for this therapy based on the results of a risk-benefit assessment. The risk-benefit assessment for using ritonavir-boosted nirmatrelvir in these patients may include factors such as medical comorbidities, body mass index, vaccination status, and the number and severity of the risk factors for severe disease. Obstetricians should be aware of potential drug-drug interactions when prescribing this agent.

Lactation is not a contraindication for the use of ritonavir-boosted nirmatrelvir. There are no data on the use of nirmatrelvir in lactating people, but the data from animal studies are reassuring. In a prebirth-to-lactation study, an 8% decrease in body weight was observed on Postnatal Day 17 in the offspring of rats who received nirmatrelvir and had systemic exposures that were 8 times higher than the clinical exposures at the authorized human dose. This reduction in body weight was not seen in the offspring of rats that had exposures that were 5 times higher than the clinical exposures at the authorized human dose.[3]

Studies of infants who were exposed to ritonavir through breast milk suggest that the amount of ritonavir that transfers through breast milk is negligible and not considered clinically significant.[32] The decision to

feed breast milk while taking ritonavir-boosted nirmatrelvir should take into consideration the benefits of breastfeeding, the need for the medication, any underlying risks of infant exposure to the drug, and the potential adverse outcomes of COVID-19.

Considerations in Children

For information on using ritonavir-boosted nirmatrelvir in pediatric patients, see Special Considerations in Children, Therapeutic Management of Nonhospitalized Children With COVID-19, and Therapeutic Management of Hospitalized Children With COVID-19.

Clinical Data

The EPIC-HR study was a multinational randomized trial that compared the use of ritonavir-boosted nirmatrelvir PO twice daily for 5 days to placebo in nonhospitalized patients aged ≥18 years with mild to moderate COVID-19 who were at high risk of clinical progression. Eligible patients were randomized within 5 days of symptom onset, were not vaccinated against COVID-19, and had at least 1 risk factor for progression to severe disease.[4] Patients were excluded if they used medications that were either highly dependent upon CYP3A4 for clearance or strong inducers of CYP3A4.

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

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

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

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

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

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

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

This is not a comprehensive list of all the medications that are not expected to have clinically relevant interactions with ritonavir-boosted nirmatrelvir.[a]

Medications Without Clinically Relevant Interactions

These medications may be coadministered without dose adjustment and without increased monitoring.[a] This list is not inclusive of all noninteracting medications within each drug category.

Acid reducers
- Famotidine
- Omeprazole
- Pantoprazole

Allergy
- Cetirizine
- Diphenhydramine
- Fexofenadine
- Loratadine

Anti-infectives
- Azithromycin
- Cidofovir
- Hydroxychloroquine
- Tecovirimat
- Valacyclovir

Cardiovascular
- Aspirin
- Atenolol
- Carvedilol
- Furosemide
- Hydrochlorothiazide
- Irbesartan
- Isosorbide dinitrate
- Lisinopril

Cardiovascular, continued
- Losartan
- Metoprolol
- Prasugrel

Diabetes
- Empagliflozin
- Insulin
- Metformin
- Pioglitazone

Immunosuppressants
- Abrocitinib
- Baricitinib
- Methotrexate
- Mycophenolate
- Prednisone

Lipid-modifiers
- Ezetimibe
- Pitavastatin
- Pravastatin

Migraine
- Frovatriptan
- Naratriptan
- Rizatriptan
- Sumatriptan

Neuropsychiatric
- Amitriptyline
- Bupropion
- Citalopram
- Duloxetine
- Escitalopram
- Fluoxetine
- Gabapentin
- Lorazepam
- Nortriptyline
- Olanzapine
- Paroxetine
- Sertraline
- Venlafaxine

Pain
- Acetaminophen
- Aspirin
- Codeine
- Ibuprofen
- Meloxicam
- Naproxen

Respiratory
- Corticosteroids (inhaled)
- Formoterol
- Montelukast

Miscellaneous
- Allopurinol
- Contraceptives (oral)[b]
- Cyclobenzaprine
- Donepezil
- Enoxaparin
- Finasteride
- Levothyroxine
- Most monoclonal antibody products[c]
- Ondansetron

Medications Without Clinically Relevant Interactions, continued
[a] This list is primarily based on the most common medication searches by U.S. users on the Liverpool COVID-19 Drug Interactions website between January 1 and July 31, 2022 (internal communication, August 2022).
[b] The FDA EUA for ritonavir-boosted nirmatrelvir suggests that individuals who use contraceptive products containing ethinyl estradiol consider using a backup, nonhormonal contraceptive method because coadministration may result in low ethinyl estradiol levels. However, the low level is not expected to be clinically significant during the 5 days of therapy. The progestin concentration of a combined hormonal contraceptive is expected to remain similar or increase with coadministration, which would maintain the effectiveness of the oral contraceptive.
[c] Ritonavir-boosted nirmatrelvir interacts with certain conjugated monoclonal antibodies, such as those conjugated to the drug monomethyl auristatin E (or vedotin). These include brentuximab vedotin, enfortumab vedotin, polatuzumab vedotin, and tisotumab vedotin. Before coadministering ritonavir-boosted nirmatrelvir and any of these conjugated monoclonal antibodies, refer to the drug's FDA prescribing information and consult with the patient's specialist providers as needed.
Key: EUA = Emergency Use Authorization; FDA = Food and Drug Administration

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

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

Longer treatment courses of ritonavir-boosted nirmatrelvir are not authorized by the current Food and Drug Administration (FDA) Emergency Use Authorization (EUA), and there are insufficient data on the efficacy of administering a second treatment course in cases where SARS-CoV-2 viral rebound is suspected. The guidance in this document is based on the drug-drug interaction potential of the FDA-authorized 5-day course of ritonavir-boosted nirmatrelvir.

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

Identifying Drug-Drug Interactions

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

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

- Quick reference lists:
  - Box 1 lists select outpatient medications that are not expected to have clinically relevant interactions with ritonavir-boosted nirmatrelvir.
  - Box 2 lists select outpatient medications that have clinically relevant drug-drug interactions with ritonavir-boosted nirmatrelvir.
- Web-based drug-drug interaction checker:
  - The Liverpool COVID-19 Drug Interactions website

- Tables with guidance on managing specific drug-drug interactions:
  - The University of Waterloo/University of Toronto drug interaction guide
  - The FDA EUA fact sheet and checklist for ritonavir-boosted nirmatrelvir

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

Management Strategies for Drug-Drug Interactions

Consider the magnitude and significance of the potential drug-drug interaction when choosing management strategies for patients who will be receiving ritonavir-boosted nirmatrelvir. Potential strategies include:

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

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

Patients should be counseled about ritonavir-boosted nirmatrelvir's drug-drug interaction potential and the signs and symptoms of potential adverse effects. If ritonavir-boosted nirmatrelvir is prescribed to patients who take certain recreational drugs, those patients will require counseling and careful monitoring for adverse effects.

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

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

<table>
<tr><th colspan="4">Prescribe Alternative COVID-19 Therapy</th></tr>
<tr><td colspan="4">For these medications, management strategies are not possible or feasible, or the risks outweigh the potential benefits.</td></tr>
<tr>
<td>Anticonvulsants
• Carbamazepine
• Phenobarbital
• Phenytoin
• Primidone
Anti-infectives
• Glecaprevir/pibrentasvir
• Rifampin
• Rifapentine</td>
<td>Immunosuppressants
• Voclosporin
Cardiovascular
• Amiodarone
• Clopidogrel[a,b]
• Disopyramide
• Dofetilide
• Dronedarone
• Eplerenone
• Flecainide</td>
<td>Cardiovascular, continued
• Ivabradine
• Propafenone
• Quinidine
Neuropsychiatric
• Clozapine
• Lurasidone
• Midazolam (oral)
• Pimozide</td>
<td>Pulmonary hypertension
• Sildenafil
• Tadalafil
• Vardenafil
Miscellaneous
• Bosentan
• Certain chemotherapeutic agents[c]
• Ergot derivatives
• Lumacaftor/ivacaftor
• St. John's wort
• Tolvaptan</td>
</tr>
</table>

Temporarily Withhold Concomitant Medication, if Clinically Appropriate

Withhold these medications during ritonavir-boosted nirmatrelvir treatment and for at least 2–3 days after treatment completion. They may need to be withheld for longer if the patient is an adult of advanced age or the medication has a long half-life. If withholding is not clinically appropriate, use an alternative concomitant medication or COVID-19 therapy.

Anticoagulants
- Rivaroxaban[d]

Anti-infectives
- Erythromycin

BPH
- Alfuzosin
- Silodosin

Cardiovascular
- Aliskiren
- Ranolazine
- Ticagrelor[b]
- Vorapaxar

Immunosuppressants[e]
- Everolimus
- Sirolimus
- Tacrolimus

Lipid-modifiers
- Atorvastatin[f]
- Lomitapide
- Lovastatin[f]
- Rosuvastatin[f]
- Simvastatin[f]

Migraine
- Eletriptan
- Rimegepant
- Ubrogepant

Neuropsychiatric
- Suvorexant
- Triazolam[g]

Erectile dysfunction
- Avanafil

Respiratory
- Salmeterol

Miscellaneous
- Certain chemotherapeutic agents[c]
- Colchicine[h]
- Finerenone
- Flibanserin
- Naloxegol

Adjust Concomitant Medication Dose and Monitor for Adverse Effects

Consult the Liverpool COVID-19 Drug Interactions website or the University of Waterloo/University of Toronto drug interaction guide for specific dosing recommendations.[i] If the dose of the concomitant medication cannot be adjusted, withhold the medication (if clinically appropriate) or use an alternative concomitant medication or COVID-19 therapy.

Anticoagulants
- Apixaban
- Dabigatran
- Edoxaban

Anti-infectives
- Clarithromycin
- Itraconazole
- Ketoconazole
- Maraviroc
- Rifabutin

BPH
- Tamsulosin

Cardiovascular
- Cilostazol
- Digoxin
- Mexiletine

Diabetes
- Saxagliptin

Erectile dysfunction
- Sildenafil
- Tadalafil
- Vardenafil

Immunosuppressants
- Cyclosporine[e]
- Dexamethasone[j]
- Fedratinib
- Ruxolitinib
- Tofacitinib
- Upadacitinib

Migraine
- Almotriptan[h]

Neuropsychiatric
- Alprazolam[g]
- Aripiprazole
- Brexpiprazole
- Buspirone
- Cariprazine
- Chlordiazepoxide[g]
- Clobazam[g]
- Clonazepam[g]
- Clorazepate[g]

Neuropsychiatric, continued
- Diazepam[g]
- Estazolam[g]
- Flurazepam[g]
- Iloperidone
- Lumateperone
- Pimavanserin
- Quetiapine
- Trazodone

Pain
- Fentanyl
- Hydrocodone
- Oxycodone

Pulmonary hypertension
- Riociguat

Miscellaneous
- Certain chemotherapeutic agents[c]
- Darifenacin
- Elexacaftor/tezacaftor/ivacaftor
- Eluxadoline
- Ivacaftor
- Solifenacin
- Tezacaftor/ivacaftor

Continue Concomitant Medication and Monitor for Adverse Effects			
Pre-emptive dose adjustment is not required but may be considered based on an individualized assessment of the patient's risk for adverse reactions. Educate patients about potential adverse effects. Consult the Liverpool COVID-19 Drug Interactions website or the University of Waterloo/University of Toronto drug interaction guide for monitoring guidance and dose adjustment information as needed.[i]			
Anticoagulants • Warfarin **Anti-infectives** • Brincidofovir[k] • Cobicistat- or ritonavir-boosted antiretrovirals • Isavuconazole • Posaconazole • Voriconazole **BPH** • Doxazosin • Terazosin	**Diabetes** • Glyburide **Cardiovascular** • Amlodipine • Diltiazem • Felodipine • Nifedipine • Sacubitril • Valsartan • Verapamil **Migraine** • Zolmitriptan	**Neuropsychiatric** • Haloperidol • Hydroxyzine • Mirtazapine • Risperidone • Ziprasidone • Zolpidem **Pain** • Buprenorphine • Hydromorphone • Methadone • Morphine • Tramadol	**Miscellaneous** • Certain chemotherapeutic agents[c] • Certain conjugated monoclonal antibodies[l] • Oxybutynin

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

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

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

[d] For patients who are at high risk of arterial or venous thrombosis (e.g., those who had a stroke within the past 3 months with a CHA2DS2-VASc score of 7–9 or a pulmonary embolism within the past month), consult the primary or specialty provider and consider using an alternative anticoagulant such as LMWH or an alternative COVID-19 therapy. For patients with a lower risk for arterial or venous thrombosis, clinicians may consider administering low-dose aspirin while rivaroxaban is being withheld.

[e] The use of another COVID-19 therapy may need to be considered. These immunosuppressants have significant drug-drug interaction potential with ritonavir, and they **should not be used** if close monitoring, including therapeutic drug monitoring, is not feasible. Consult a patient's specialist providers before coadministering these immunosuppressants and ritonavir-boosted nirmatrelvir. See the American Society of Transplantation statement for more information.

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

[g] The guidance on managing drug-drug interactions between certain benzodiazepines and ritonavir-boosted nirmatrelvir can vary significantly between resources. The guidance in this table is based on the FDA EUA fact sheet for ritonavir-boosted nirmatrelvir. Note that abrupt discontinuation or rapid dose reduction of benzodiazepines may precipitate an acute withdrawal reaction.[2] The risk is greatest for patients who have been using high doses of benzodiazepines over an extended period.

[h] For patients with hepatic or renal impairment, do not coadminister this medication with ritonavir-boosted nirmatrelvir.

[i] For medications that are not included on the Liverpool COVID-19 Drug Interactions website or the University of Waterloo/University of Toronto drug interaction guide, refer to the FDA labels for information on coadministering these medications with ritonavir or other strong CYP3A4 and/or P-gp inhibitors.

Continue Concomitant Medication and Monitor for Adverse Effects, continued
[j] Dexamethasone exposure is expected to increase 2.60-fold when dexamethasone is coadministered with ritonavir-boosted nirmatrelvir.[3] Clinicians should weigh the risks and benefits of continuing the patient's normal dose of dexamethasone (while monitoring for AEs) versus decreasing the dose. Patients who are receiving higher doses of dexamethasone will be at a greater risk of AEs.
[k] Patients should take ritonavir-boosted nirmatrelvir at least 3 hours after receipt of brincidofovir.
[l] Ritonavir-boosted nirmatrelvir interacts with certain conjugated monoclonal antibodies, such as those conjugated to the drug monomethyl auristatin E (or vedotin). These include brentuximab vedotin, enfortumab vedotin, polatuzumab vedotin, and tisotumab vedotin. Before coadministering ritonavir-boosted nirmatrelvir and any of these conjugated monoclonal antibodies, refer to the drug's FDA prescribing information and consult with the patient's specialist providers as needed.
Key: AE = adverse effect; BPH = benign prostatic hyperplasia; CHA2DS2-VASc = congestive heart failure, hypertension, age, diabetes, stroke, vascular disease; CYP = cytochrome P450; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; LMWH = low-molecular-weight heparin; P-gp = P-glycoprotein

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Molnupiravir

Last Updated: September 26, 2022

Molnupiravir is the oral prodrug of beta-D-N4-hydroxycytidine (NHC), a ribonucleoside that has shown antiviral activity against SARS-CoV-2 in vitro and in clinical trials.[1,2] NHC uptake by viral RNA-dependent RNA-polymerases results in viral mutations and lethal mutagenesis.[3,4] On December 23, 2021, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for molnupiravir for the treatment of adults with mild to moderate COVID-19 who are within 5 days of symptom onset, who are at high risk of progressing to severe disease, and for whom alternative antiviral therapies are not accessible or clinically appropriate.[5,6]

As a mutagenic ribonucleoside antiviral agent, there is a theoretical risk that molnupiravir will be metabolized by the human host cell and incorporated into the host DNA, leading to mutations. Molnupiravir has been evaluated in 2 in vivo rodent mutagenicity assays. One study produced equivocal results. In the other study, there was no evidence for mutagenicity.[6] The FDA concluded that, based on the available genotoxicity data and the 5-day duration of treatment, molnupiravir has a low risk for genotoxicity.[6] In addition, there have been concerns about the potential effects of molnupiravir on SARS-CoV-2 mutation rates; the FDA has required that the manufacturer monitor genomic databases for the emergence of SARS-CoV-2 variants.

Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using **molnupiravir 800 mg** orally (PO) twice daily for 5 days as an alternative therapy in nonhospitalized patients aged ≥18 years with mild to moderate COVID-19 who are at high risk of disease progression **ONLY** when ritonavir-boosted nirmatrelvir (Paxlovid) and remdesivir are not available, feasible to use, or clinically appropriate; treatment should be initiated as soon as possible and within 5 days of symptom onset **(CIIa)**.
- The Panel **recommends against** the use of **molnupiravir** for the treatment of COVID-19 in pregnant patients unless there are no other options and therapy is clearly indicated **(AIII)**.
- People who engage in sexual activity that may result in conception should use effective contraception during and following treatment with molnupiravir. For more details, see Considerations in Sexually Active Individuals below.

Molnupiravir may be used in patients who are hospitalized for a diagnosis other than COVID-19, provided they have mild to moderate COVID-19 and are at high risk of progressing to severe disease. For the Panel's recommendations on preferred and alternative antiviral therapies for outpatients with COVID-19, see Therapeutic Management of Nonhospitalized Adults With COVID-19.

Rationale

The MOVe-OUT trial enrolled high-risk, unvaccinated, nonhospitalized adults and reported that molnupiravir reduced the rate of hospitalization or death among these patients by 31% compared to placebo.[7] However, this trial occurred before the emergence of the Omicron variant and its subvariants. A secondary analysis of the patients who required hospitalization during the trial found a reduced need for respiratory interventions among those who were randomized to receive molnupiravir compared to those who received placebo.[8] Molnupiravir has shown activity against the Omicron subvariants in vitro and in animal studies.[2,9-11]

Although the different COVID-19 treatment options have not been directly compared in clinical trials, the Panel recommends using molnupiravir only when ritonavir-boosted nirmatrelvir and remdesivir are not available or cannot be given, because molnupiravir appears to have lower efficacy than these other options.

Whether molnupiravir reduces the risk of hospitalization or death in people who are vaccinated and at high risk of progressing to severe COVID-19 is unclear. Some observational studies have evaluated the effect of molnupiravir in nonhospitalized or hospitalized adults who are at high risk of progressing to severe disease, including some patients who received COVID-19 vaccines, but these studies have limitations.[12-14] For treatment considerations for vaccinated individuals, see Therapeutic Management of Nonhospitalized Adults With COVID-19.

The Panel **recommends against** the use of **molnupiravir** for the treatment of COVID-19 in pregnant patients unless there are no other options and therapy is clearly indicated **(AIII)**. For more details, see Considerations in Pregnancy below.

Additional Considerations

- Patients should complete the 5-day treatment course of molnupiravir. It is unknown whether a shorter course is less effective or associated with the emergence of molnupiravir-resistant mutations.
- If a patient requires hospitalization after starting treatment, the full treatment course of molnupiravir can be completed at the health care provider's discretion.
- There are no data on using combination antiviral therapies or combinations of antiviral agents and anti-SARS-CoV-2 monoclonal antibodies for the treatment of nonhospitalized patients with COVID-19. Clinical trials are needed to determine whether combination therapy has a role in the treatment of SARS-CoV-2 infection.
- Patients who are severely immunocompromised can experience prolonged periods of SARS-CoV-2 replication, which may lead to rapid viral evolution. There are theoretical concerns that using a single antiviral agent in these patients may produce antiviral-resistant viruses. Additional studies are needed to assess this risk. The role of combination antiviral therapy in treating patients who are severely immunocompromised is not yet known. See Special Considerations in People Who Are Immunocompromised for more information.
- It is not yet known how often viral rebound occurs in patients who have completed treatment with molnupiravir.

Considerations in Sexually Active Individuals

For individuals of childbearing potential, clinicians should assess the patient's pregnancy status before initiating molnupiravir.

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

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

Considerations in Pregnancy

The Panel **recommends against** the use of **molnupiravir** for the treatment of COVID-19 in pregnant patients unless there are no other options and therapy is clearly indicated **(AIII)**.

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

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

Considerations in Children

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

Monitoring, Adverse Effects, and Drug-Drug Interactions

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

Clinical Data

MOVe-OUT was a multinational, Phase 3 trial that evaluated the use of molnupiravir in unvaccinated, nonhospitalized adults with mild to moderate COVID-19 who were at high risk of progressing to severe COVID-19 and enrolled within 5 days of symptom onset. The trial was conducted before the emergence of the Omicron variant and its subvariants. Pregnant people, lactating people, and children were excluded from the study. Participants were randomized to receive molnupiravir 800 mg PO every 12 hours for 5 days or placebo.[7] The primary composite outcome was all-cause hospitalization (defined as a hospital stay >24 hours) or death by Day 29.

The final analysis included 1,433 participants; the median age was 43 years (with 17% aged >60 years). Forty-nine percent of the participants were men, 57% were White, 50% were Hispanic/Latinx, and 5% were Black or African American.[7] Among the participants, 74% had a body mass index ≥30 and 16% had diabetes. The time from COVID-19 symptom onset to randomization was ≤3 days in 48% of the participants.

By Day 29, the use of molnupiravir reduced the risk of hospitalization or death by 31%, with 48 of 709 participants (6.8%) in the molnupiravir arm experiencing hospitalization or death compared with 68 of 699 participants (9.7%) in the placebo arm (-3.0% adjusted difference; 95% CI, -5.9% to -0.1%).[7] The molnupiravir arm had 1 death, and the placebo arm had 9 deaths. There were no significant differences between the arms in the proportion of participants who experienced adverse events or serious adverse events. A secondary analysis of data from the patients who were hospitalized during the trial revealed

that the use of molnupiravir reduced the risk of requiring respiratory interventions (conventional or high-flow oxygen delivery or noninvasive or invasive mechanical ventilation) by 21%.[8]

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Anti-SARS-CoV-2 Monoclonal Antibodies

Last Updated: December 28, 2022

Monoclonal antibodies (mAbs) that target the SARS-CoV-2 spike protein have been shown to have clinical benefits in treating SARS-CoV-2 infection. However, laboratory studies have found that the activity of anti-SARS-CoV-2 mAbs against specific variants and subvariants can vary dramatically. Because of this, these products are not expected to be effective treatments for COVID-19 in areas where the circulating variants and subvariants are resistant to mAbs.

Recommendation

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of anti-SARS-CoV-2 mAbs for the treatment of COVID-19 **(AIII)** because the dominant Omicron subvariants in the United States are not expected to be susceptible to these products.
- For the Panel's recommendations on treating nonhospitalized patients with COVID-19, see Therapeutic Management of Nonhospitalized Adults With COVID-19 and Therapeutic Management of Nonhospitalized Children With COVID-19.

Anti-SARS-CoV-2 Monoclonal Antibodies That Have Received Emergency Use Authorizations

Four anti-SARS-CoV-2 mAb products (bamlanivimab plus etesevimab, casirivimab plus imdevimab, sotrovimab, and bebtelovimab) received Emergency Use Authorizations from the Food and Drug Administration for the treatment of outpatients with mild to moderate COVID-19. However, they are not currently authorized for use in the United States because the dominant circulating Omicron subvariants are not expected to be susceptible to these products. See the Centers for Disease Control and Prevention COVID Data Tracker for regular updates on the regional proportions of SARS-CoV-2 variants in the United States.

Tixagevimab plus cilgavimab (Evusheld) is the only anti-SARS-CoV-2 mAb product that is currently authorized for use as pre-exposure prophylaxis (PrEP). These recombinant human mAbs bind to nonoverlapping epitopes of the spike protein receptor-binding domain of SARS-CoV-2. Many Omicron subvariants, including the dominant Omicron subvariants in the United States, are expected to be less susceptible to tixagevimab plus cilgavimab. See Prevention of SARS-CoV-2 Infection for more information.

Table A. SARS-CoV-2 Variants Currently or Recently Circulating in the United States and Their Susceptibility to Anti-SARS-CoV-2 Monoclonal Antibodies

For information on SARS-CoV-2 variants that were previously circulating in the United States, see the Guidelines Archive.

WHO Label and Pango Lineage	BEB		TIX Plus CIL[a]		BAM Plus ETE		CAS Plus IMD		SOT	
	In Vitro Susceptibility[b]	Anticipated Clinical Activity	In Vitro Susceptibility[b]	Anticipated Clinical Activity	In Vitro Susceptibility[b]	Anticipated Clinical Activity	In Vitro Susceptibility[b]	Anticipated Clinical Activity	In Vitro Susceptibility[b]	Anticipated Clinical Activity
Omicron BA.5	No change	Active	Moderate reduction	Active	Marked reduction	Unlikely to be active	Marked reduction	Unlikely to be active	Marked reduction	Unlikely to be active
Omicron BA.4.6/ BF.7	No change	Active	Marked reduction	Unlikely to be active	Marked reduction	Unlikely to be active	Marked reduction	Unlikely to be active	Marked reduction	Unlikely to be active
Omicron BQ.1	Marked reduction	Unlikely to be active	Marked reduction	Unlikely to be active	Marked reduction	Unlikely to be active	Marked reduction	Unlikely to be active	Marked reduction	Unlikely to be active
Omicron BQ.1.1	Marked reduction	Unlikely to be active	Marked reduction	Unlikely to be active	Marked reduction	Unlikely to be active	Marked reduction	Unlikely to be active	Marked reduction	Unlikely to be active
Omicron XBB	Marked reduction[1,2]	Unlikely to be active	Marked reduction	Unlikely to be active	Marked reduction	Unlikely to be active	Marked reduction	Unlikely to be active	Marked reduction	Unlikely to be active

[a] Other variants are expected to be resistant to TIX plus CIL (e.g., BA.5.2.6, BF.11, BA.2.75.2). However, these variants currently represent a small proportion of the circulating variants in the United States.

[b] This information is based on the fold reduction in susceptibility reported in the FDA EUAs.[3-7]

Key: BAM = bamlanivimab; BEB = bebtelovimab; CAS = casirivimab; CIL = cilgavimab; ETE = etesevimab; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; IMD = imdevimab; SOT = sotrovimab; TIX = tixagevimab; WHO = World Health Organization

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Table 4b. Anti-SARS-CoV-2 Monoclonal Antibodies: Selected Clinical Data

Last Updated: April 29, 2022

This table describes only the clinical trials that have evaluated anti-SARS-CoV-2 mAbs for the treatment of COVID-19. Please see Prevention of SARS-CoV-2 Infection for a discussion of the clinical trials that have evaluated anti-SARS-CoV-2 mAbs for PEP of SARS-CoV-2 infection.

Methods	Results	Limitations and Interpretation
BLAZE-1: Double-Blind RCT of Bamlanivimab 700 mg Plus Etesevimab 1,400 mg in Nonhospitalized Patients With Mild to Moderate COVID-19 in the United States and Puerto Rico[1]		

Key Inclusion Criteria
• Aged ≥12 years
• At high risk for severe COVID-19 or hospitalization
Interventions
• Within 3 days of a positive SARS-CoV-2 test result, single infusion of:
  • BAM 700 mg plus ETE 1,400 mg (n = 511)
  • Placebo (n = 258)
Primary Endpoint
• COVID-19-related hospitalization (defined as ≥24 hours of acute care) or death from any cause by Day 29
	Participant Characteristics
	• Median age 56 years; 30% aged ≥65 years; 53% women
	• 87% White, 27% Hispanic/Latinx, 8% Black/African American
	• Mean duration of symptoms was 4 days
	• 76% with mild COVID-19, 24% with moderate COVID-19
	Primary Outcomes
	• COVID-19-related hospitalizations or all-cause deaths by Day 29: 4 (0.8%) in BAM plus ETE arm vs. 15 (5.8%) in placebo arm (change of -5.0%; 95% CI, -8.0% to -2.1%; $P < 0.001$)
	• All-cause deaths by Day 29: 0 in BAM plus ETE arm vs. 4 (1.6%) in placebo arm
		Key Limitation
		• Conducted before widespread circulation of the Omicron VOC
		Interpretation
		• Compared to placebo, BAM plus ETE significantly reduced the number of COVID-19-related hospitalizations and all-cause deaths in high-risk patients.

BLAZE-4, Treatment Arms 9–11: Double-Blind RCT of Bamlanivimab Plus Etesevimab Plus Bebtelovimab Versus Bebtelovimab Alone Versus Placebo in Low-Risk, Nonhospitalized Patients With Mild to Moderate COVID-19[2]		

Key Inclusion Criteria
• Aged 18–64 years
• No risk factors for progression to severe COVID-19
Key Exclusion Criteria
• ≥1 of the following:
  • SpO_2 ≤93% on room air
  • Respiratory rate ≥30 breaths/min
  • Heart rate ≥125 bpm
	Participant Characteristics
	• Median age 35 years; 56% women
	• 36% Hispanic/Latinx, 19% Black/African American
	• Mean duration of symptoms prior to enrollment was 3.6 days
	Primary Outcomes
	• Proportion with PHVL:
	  • 13% in BAM plus ETE plus BEB arm vs. 21% in placebo arm ($P = 0.098$), with a relative reduction of 38% (95% CI, -9% to 65%)
		Key Limitations
		• Only low-risk patients included
		• Not powered to assess hospitalizations and deaths
		• Conducted before widespread circulation of the Omicron VOC
		Interpretations
		• There were no differences in the proportion of patients with PHVL across the arms.

Methods	Results	Limitations and Interpretation
BLAZE-4, Treatment Arms 9–11: Double-Blind RCT of Bamlanivimab Plus Etesevimab Plus Bebtelovimab Versus Bebtelovimab Alone Versus Placebo in Low-Risk, Nonhospitalized Patients With Mild to Moderate COVID-19[2], continued		

Interventions
• Within 3 days of a positive SARS-CoV-2 test result, single infusion of:
  • BAM 700 mg plus ETE 1,400 mg plus BEB 175 mg (n = 127)
  • BEB 175 mg (n = 125)
  • Placebo (n = 128)
Primary Endpoint
• Proportion of patients with PHVL (defined as SARS-CoV-2 VL >5.82 $\log_{10}$ by Day 7)
Key Secondary Endpoints
• Mean change in VL from baseline to Days 3, 5, 7, and 11
• COVID-19-related hospitalization or death from any cause by Day 29
• Time to sustained symptom resolution
	• 14% in BEB arm vs. 21% in placebo arm ($P = 0.147$), with a relative reduction of 34% (95% CI, -15% to 62%)
	Secondary Outcomes
	• Mean decline in VL greater in mAb arms vs. placebo arm at Day 5 but not at Days 3, 7, or 11
	• COVID-19-related hospitalizations or all-cause deaths by Day 29:
	  • 3 (2.4%) in BAM plus ETE plus BEB arm, including 1 death
	  • 2 (1.6%) in BEB arm
	  • 2 (1.6%) in placebo arm
	• Median time to sustained symptom resolution:
	  • 7 days in BAM plus ETE plus BEB arm vs. 8 days in placebo arm ($P = 0.289$)
	  • 6 days in BEB arm vs. 8 days in placebo arm ($P = 0.003$)
		• Few COVID-19-related hospitalizations or deaths from any cause occurred by Day 29 across the arms, as is expected for a population of individuals who were at low risk of severe COVID-19.
		• Compared to placebo, the median time to sustained symptom resolution was shorter in the BEB arm.

BLAZE-4, Treatment Arms 12 and 13: Open-Label RCT of Bamlanivimab Plus Etesevimab Plus Bebtelovimab and Bebtelovimab Alone in High-Risk, Nonhospitalized Patients With Mild to Moderate COVID-19[2]		

Key Inclusion Criteria
• Aged ≥12 years
• Weight ≥40 kg
• ≥1 risk factor for progression to severe COVID-19
Key Exclusion Criteria
• ≥1 of the following:
  • SpO_2 ≤93% on room air
  • Respiratory rate ≥30 breaths/min
  • Heart rate ≥125 bpm
Interventions
• Within 3 days of a positive SARS-CoV-2 test result, single infusion of:
	Participant Characteristics
	• Median age 50 years; 52% women
	• 18% Hispanic/Latinx, 18% Black/African American
	• Mean duration of symptoms prior to enrollment was 4.7 days
	• 21% had at least 1 dose of COVID-19 vaccine
	Efficacy Outcomes
	• COVID-19-related hospitalization or death from any cause by Day 29: 2 (4%) in BAM plus ETE plus BEB arm vs. 3 (3%) in BEB arm
	• Mean decline in VL greater in BAM plus ETE plus BEB arm vs. BEB arm at Day 5 but not at Days 3, 7, or 11
		Key Limitations
		• Open-label study
		• No placebo arm
		• Not powered to assess hospitalizations and deaths
		• Conducted before widespread circulation of the Omicron VOC
		Interpretation
		• There was no difference in the proportion of patients who were hospitalized or who died between the arms.

Methods	Results	Limitations and Interpretation
BLAZE-4, Treatment Arms 12 and 13: Open-Label RCT of Bamlanivimab Plus Etesevimab Plus Bebtelovimab and Bebtelovimab Alone in High-Risk, Nonhospitalized Patients With Mild to Moderate COVID-19[2], continued		
• BAM 700 mg plus ETE 1,400 mg plus BEB 175 mg (n = 50) • BEB 175 mg (n = 100) **Efficacy Endpoints** • COVID-19-related hospitalization or death from any cause by Day 29 • Mean change in VL from baseline to Days 3, 5, 7, and 11		
Double-Blind RCT of Casirivimab Plus Imdevimab in Nonhospitalized Patients With Mild to Moderate COVID-19[3]		

Key Inclusion Criteria
• Aged ≥18 years
• Laboratory-confirmed SARS-CoV-2 infection
• Symptom onset within 7 days of randomization
• For patients included in the modified full analysis only:
  • ≥1 risk factor for severe COVID-19
  • Positive SARS-CoV-2 RT-PCR result at baseline
Interventions
• Single IV infusion of:
  • CAS 600 mg plus IMD 600 mg (n = 736) or placebo (n = 748)
  • CAS 1,200 mg plus IMD 1,200 mg (n = 1,355) or placebo (n = 1,341)
Primary Endpoint
• ≥1 COVID-19-related hospitalization or death from any cause by Day 29
	Participant Characteristics
	• Median age 50 years
	• 35% Hispanic/Latinx, 5% Black/African American
	• Median duration of symptoms prior to enrollment was 3 days
	Primary Outcomes
	• COVID-19-related hospitalizations or all-cause deaths through Day 29:
	  • 7 (1.0%) in CAS 600 mg plus IMD 600 mg arm vs. 24 (3.2%) in placebo arm ($P = 0.002$)
	  • 18 (1.3%) in CAS 1,200 mg plus IMD 1,200 mg arm vs. 62 (4.6%) in placebo arm ($P < 0.001$)
	• All-cause deaths:
	  • 1 (0.1%) in CAS 600 mg plus IMD 600 mg arm vs. 1 (0.1%) in placebo arm
	  • 1 (< 0.1%) in CAS 1,200 mg plus IMD 1,200 mg arm vs. 3 (0.2%) in placebo arm
		Key Limitation
		• Conducted before widespread circulation of the Omicron VOC
		Interpretation
		• Compared to placebo, CAS 600 mg plus IMD 600 mg and CAS 1,200 mg plus IMD 1,200 mg reduced the risk of COVID-19-related hospitalizations or all-cause deaths in patients with mild to moderate COVID-19.

Methods	Results	Limitations and Interpretation
COMET-ICE: Double-Blind RCT of Sotrovimab in Nonhospitalized Patients With Mild to Moderate COVID-19 in Brazil, Canada, Peru, Spain, and the United States[4]		
Key Inclusion Criteria • Aged ≥18 years • ≥1 comorbidity or aged ≥55 years • Positive SARS-CoV-2 RT-PCR or antigen test result • Symptom onset ≤5 days before enrollment **Key Exclusion Criteria** • Hospitalized or required supplemental oxygen • Severely immunocompromised **Interventions** • SOT 500 mg IV (n = 528) • Placebo (n = 529) **Primary Endpoint** • Hospitalization or death from any cause by Day 29	**Participant Characteristics** • Median age 53 years; 20% aged ≥65 years; 54% women • 65% Hispanic/Latinx, 8% Black/African American • 63% with obesity; 22% with DM; 17% with moderate to severe asthma **Primary Outcome** • Hospitalizations or all-cause deaths by Day 29: 6 (1%) in SOT arm vs. 30 (6%) in placebo arm, including 2 deaths (adjusted relative risk 0.21; 95% CI, 0.09–0.50; absolute difference -4.53%; 95% CI, -6.70% to -2.37%; $P < 0.001$)	**Key Limitation** • Conducted before widespread circulation of the Omicron VOC **Interpretation** • Compared to placebo, SOT reduced the incidence of all-cause hospitalizations and deaths among patients with mild to moderate COVID-19.

Key: BAM = bamlanivimab; bpm = beats per minute; BEB = bebtelovimab; CAS = casirivimab; DM = diabetes mellitus; ETE = etesevimab; IMD = imdevimab; IV = intravenous; mAb = monoclonal antibody; PEP = post-exposure prophylaxis; PHVL = persistently high viral load; RCT = randomized controlled trial; RT-PCR = reverse transcription polymerase chain reaction; SOT = sotrovimab; SpO_2 = oxygen saturation; VL = viral load; VOC = variant of concern

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COVID-19 Convalescent Plasma

Last Updated: December 1, 2022

Plasma from donors who have recovered from COVID-19 (regardless of vaccination status) may contain antibodies to SARS-CoV-2 that could help suppress viral replication.[1] In August 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for COVID-19 convalescent plasma (CCP) for the treatment of hospitalized patients with COVID-19. The EUA was subsequently revised. The current EUA limits the authorization to the use of CCP products that contain high levels of anti-SARS-CoV-2 antibodies (i.e., high-titer products) for the treatment of outpatients or inpatients with COVID-19 who have immunosuppressive disease or who are receiving immunosuppressive treatment. The testing criteria used to identify high-titer CCP products was also revised.[2]

The use of CCP should be limited to high-titer products. Products that are not labeled "high titer" should not be used.

Recommendations

Patients Who Are Immunocompromised

- There is insufficient evidence for the Panel to recommend either for or against the use of high-titer CCP for the treatment of COVID-19 in hospitalized or nonhospitalized patients who are immunocompromised.
    - Some Panel members would use CCP to treat an immunocompromised patient with significant symptoms attributable to COVID-19 and with signs of active SARS-CoV-2 replication and who is having an inadequate response to available therapies. In these cases, clinicians should attempt to obtain high-titer CCP from a vaccinated donor who recently recovered from COVID-19 likely caused by a SARS-CoV-2 variant similar to the variant causing the patient's illness.

Patients Who Are Immunocompetent

- The Panel **recommends against** the use of CCP for the treatment of COVID-19 in hospitalized patients who are immunocompetent **(AI)**.
- There is insufficient evidence for the Panel to recommend either for or against the use of high-titer CCP for the treatment of COVID-19 in nonhospitalized patients who are immunocompetent.

Rationale

Patients Who Are Immunocompromised

This section pertains to people who are moderately or severely immunocompromised. For examples of moderately or severely immunocompromising conditions and for a broader discussion on the therapeutic management of COVID-19 in people who are immunocompromised, see Special Considerations in People Who Are Immunocompromised.

Under the revised EUA issued on December 27, 2021, CCP is authorized for the treatment of COVID-19 in nonhospitalized or hospitalized patients who have immunosuppressive disease or are receiving immunosuppressive treatment.[2]

Evidence to support the use of CCP for the treatment of COVID-19 in patients who are

immunocompromised is limited. No randomized, adequately powered trials evaluating CCP for the treatment of COVID-19 in these patients have been published. Some subgroup analyses generated from clinical trials that enrolled patients who were immunocompromised suggested a potential benefit from the use of CCP in this population.[3-5] However, subgroup analyses need to be interpreted with caution. In the overall trial populations, there was no evidence of benefit from the use of CCP. Other clinical data from case series, retrospective case-control studies, and meta-analyses have been cited as support for the potential benefit of CCP in patients who are immunocompromised. However, the patient populations differed across studies, and the studies had design limitations, making the findings difficult to interpret.[6-14]

Despite the absence of definitive evidence, there is a physiologic rationale for the use of SARS-CoV-2 antibody-based therapies in patients who are immunocompromised. For example, these patients are at risk of having reduced antibody responses to SARS-CoV-2 infection and COVID-19 vaccination, having suboptimal control of viral replication, and progressing to severe disease.[15,16]

The emergence of SARS-CoV-2 variants further complicates any assessment of benefit from the use of CCP. Although results from some in vitro studies suggest that CCP collected from vaccinated individuals who recovered from Omicron infection exhibits neutralizing activity against certain Omicron subvariants,[17-23] extrapolation of these results to the clinical setting is challenging for the following reasons:[24]

- COVID-19 immune responses across donor populations are heterogeneous; thus, CCP products are variable.
- The tests used to qualify high-titer CCP measure anti-SARS-CoV-2 antibody titers. They do not directly measure neutralizing activity or account for currently circulating subvariants.
- Published in vitro studies that evaluated the virologic activity of CCP against the currently circulating variants used a variety of assays that are difficult to compare and interpret.[20-23,25-27]
- The pharmacokinetics and pharmacodynamics of individual CCP products are not clearly understood; therefore, determining the clinical relevance of a degree of in vitro neutralization activity is difficult.

In this context, the Panel has concluded that there is insufficient evidence for a definitive recommendation. However, given the need for treatment of COVID-19 in people who are immunocompromised, some Panel members would use CCP in certain situations (see the recommendation statement above).

Adequately powered, well-designed, and well-conducted randomized clinical trials are needed to provide more specific, evidence-based guidance on the role of CCP in the treatment COVID-19 in patients who are immunocompromised.

Hospitalized Patients Who Are Immunocompetent

Under the revised EUA, the use of CCP is not authorized for hospitalized patients who do not have immunosuppressive disease or who are not receiving immunosuppressive treatments.

Clinical data on the use of CCP for the treatment of COVID-19 in hospitalized patients who are immunocompetent, including data from several randomized trials and the U.S. Expanded Access Program for CCP, are summarized in Table 4c.

Results from the 3 largest randomized controlled trials that evaluated CCP in hospitalized patients—RECOVERY,[28] CONCOR-1,[29] and REMAP-CAP[4]—found no evidence of benefit from the use of high-titer CCP in hospitalized patients with COVID-19. All 3 were open-label trials that were stopped early due to futility.

The Panel **recommends against** the use of CCP for the treatment of COVID-19 in hospitalized patients who are immunocompetent **(AI)**.

Nonhospitalized Patients Who Are Immunocompetent

CCP is not authorized for the treatment of nonhospitalized patients with COVID-19 who do not have immunosuppressive disease or who are not receiving immunosuppressive treatment.

Data from well-designed clinical trials that evaluated the use of CCP for the treatment of nonhospitalized patients with COVID-19 prior to the emergence of the Omicron variants are conflicting. These data are summarized in Table 4c. Differences in patient populations, the placebo used (e.g., some studies used saline, and some used non-SARS-CoV-2 plasma), and CCP manufacturing and testing methods may have contributed to the disparate outcomes and difficulty in reconciling results across these clinical trials. The emergence of SARS-CoV-2 variants further complicates the assessment of benefit from the use of CCP.

There is insufficient evidence for the Panel to recommend either for or against the use of high-titer CCP for the treatment of COVID-19 in nonhospitalized patients who are immunocompetent.

Considerations in Pregnancy

The safety and efficacy of using CCP during pregnancy have not been evaluated in clinical trials, and published data on its use in pregnant individuals with COVID-19 are limited to case reports.[30] Pathogen-specific immunoglobulins (Ig) are used clinically during pregnancy to prevent infection from varicella zoster virus and rabies virus and have been used in clinical trials of congenital cytomegalovirus infection.[31,32] Pregnancy is not a reason to withhold CCP from a patient if it is otherwise indicated. The expected physiologic immunomodulation during pregnancy should not affect the decision to use CCP.

Considerations in Children

The safety and efficacy of CCP have not been systematically evaluated in pediatric patients. Published literature on its use in children is limited to case reports and case series. A few clinical trials evaluating the use of CCP in children are ongoing. The use of high-titer CCP may be considered on a case-by-case basis for hospitalized children who are immunocompromised and meet the EUA criteria for its use. CCP is not authorized by the FDA for use in patients who are immunocompetent.

As an alternative to CCP, several antiviral therapies are available for the treatment of children with COVID-19 who are at high risk of progressing to severe disease. The use of these products in children may be considered on a case-by-case basis. See Special Considerations in Children and Therapeutic Management of Hospitalized Children With COVID-19 for more information.

Monitoring and Adverse Effects

The available data suggest that serious adverse reactions following the administration of CCP are infrequent and consistent with the risks associated with plasma infusions for other indications. These risks include transfusion-transmitted infections (e.g., HIV, hepatitis B, hepatitis C), allergic reactions, anaphylactic reactions, febrile nonhemolytic reactions, transfusion-related acute lung injury, transfusion-associated circulatory overload, and hemolytic reactions. Hypothermia, metabolic complications, and post-transfusion purpura have also been described.[2,28,33]

Additional risks of CCP transfusion include a theoretical risk of antibody-dependent enhancement of SARS-CoV-2 infection. In the CONCOR-1 trial, higher levels of full transmembrane spike IgG were associated with worse outcomes, suggesting that the use of CCP with nonfunctional anti-SARS-CoV-2

antibodies may be harmful.[29] A subgroup analysis in the REMAP-CAP trial showed potential harm in patients who received CCP transfusions more than 7 days after being hospitalized.[4]

When considering the use of CCP in patients with a history of severe allergic or anaphylactic transfusion reactions, consultation with a transfusion medicine specialist is advised.

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Table 4c. COVID-19 Convalescent Plasma: Selected Clinical Data

Last Updated: December 1, 2022

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

Methods	Results	Limitations and Interpretation
REMAP-CAP: Multinational, Open-Label RCT of High-Titer CCP in Hospitalized Patients With Critical COVID-19 in Australia, Canada, the United Kingdom, and the United States[1]		

Key Inclusion Criterion
• Admitted to ICU while receiving respiratory support (HFNC oxygen, NIV, MV, ECMO) and/or vasopressor or inotrope support
Key Exclusion Criteria
• CCP contraindicated
• Death imminent
Interventions
• High-titer CCP (550 mL +/- 150 mL) within 48 hours of randomization (n = 1,084)
• Usual care (n = 916)
Primary Endpoint
• Organ support-free days by Day 21 (ordinal outcome)
Key Secondary Endpoints
• In-hospital mortality
• Mortality by Day 28 and Day 90
• Respiratory support-free days
• ICU LOS
	Participant Characteristics
	• Mean age 61 years; 68% men
	• 32% on MV
	• 29% SARS-CoV-2 antibody negative at baseline
	• 94% received corticosteroids, 45% received RDV, 39% received IL-6 inhibitors
	Primary Outcome
	• Median number of organ support-free days by Day 21: 0 days in CCP arm vs. 3 days in usual care arm (OR 0.97; 95% CrI, 0.82–1.14)
	Secondary Outcomes
	• No difference between arms in:
	  • In-hospital mortality: 37% in CCP arm vs. 38% in usual care arm
	  • Mortality by Day 28 or Day 90
	  • Median number of respiratory support-free days: 0 days in CCP arm vs. 2 days in usual care arm
	  • Median ICU LOS: 21 days in CCP arm vs. 17 days in usual care arm
		Key Limitations
		• Open-label study
		• Not all patients in CCP arm received CCP (86% received CCP as per protocol and 95% received some CCP).
		Interpretation
		• There was no benefit of CCP in hospitalized patients with critical COVID-19.

Methods	Results	Limitations and Interpretation
CONCOR-1: Multinational, Open-Label RCT of CCP for Hospitalized Patients With COVID-19 in Canada, the United States, and Brazil[2]		

Key Inclusion Criteria
• Receipt of supplemental oxygen
• Within 12 days of respiratory symptom onset
Key Exclusion Criterion
• Imminent or current intubation
Interventions
• 1–2 units CCP (approximately 500 mL) from 1–2 donors (n = 625)
• SOC (n = 313)
Primary Endpoint
• Intubation or death by Day 30
Key Secondary Endpoints
• Time to intubation or death by Day 30
• Mortality by Day 30
• ICU LOS by Day 30
• Need for renal dialysis by Day 30
• Frequency of SAEs by Day 30
	Participant Characteristics
	• Mean age 68 years; 59% men
	• 84% receiving systemic corticosteroids at enrollment
	Primary Outcome
	• Intubation or death by Day 30: 32% in CCP arm vs. 28% in SOC arm (relative risk 1.16; 95% CI, 0.94–1.43, *P* = 0.18)
	Secondary Outcomes
	• By Day 30, no difference between arms in:
	  • Time to intubation or death
	  • Mortality: 23% in CCP arm vs. 21% in SOC arm
	  • Mean ICU LOS: 4.3 days in CCP arm vs. 3.7 days in SOC arm
	  • Need for renal dialysis: 1.6% in CCP arm vs. 2.0% in SOC arm
	• Frequency of SAEs by Day 30: 33% in CCP arm vs. 26% in SOC arm
		Key Limitations
		• Open-label study
		• Trial stopped at 78% of planned enrollment after meeting prespecified futility criteria for early termination.
		Interpretation
		• There was no benefit of CCP in oxygen-dependent, hospitalized COVID-19 patients within 12 days of symptom onset.

RECOVERY: Open-Label RCT of High-Titer CCP in Hospitalized Patients in the United Kingdom[3]		

Key Inclusion Criterion
• Clinically suspected or laboratory-confirmed SARS-CoV-2 infection
Key Exclusion Criterion
• CCP contraindicated
Interventions
• Approximately 275 mL per unit of CCP with IgG against SARS-CoV-2 spike protein, with sample to cutoff ratio ≥6.0; administered as 2 units of high-titer CCP (first unit ASAP after randomization, second unit ≥12 hours later the next day) (n = 5,795)
• Usual care (n = 5,763)
	Participant Characteristics
	• Mean age 64 years; 64% men
	• 5% on MV
	• 92% received corticosteroids
	Primary Outcomes
	• No difference between arms in:
	  • Mortality: 24% in each arm
	  • Mortality in patients without detectable SARS-CoV-2 antibodies: 32% in CCP arm vs. 34% in usual care arm
	Secondary Outcomes
	• No difference between arms in:
		Key Limitation
		• Open-label study
		Interpretation
		• There was no benefit of CCP in hospitalized patients with COVID-19.

Methods	Results	Limitations and Interpretation
RECOVERY: Open-Label RCT of High-Titer CCP in Hospitalized Patients in the United Kingdom[3], continued		
Primary Endpoint • All-cause mortality by Day 28 **Key Secondary Endpoints** • Time to hospital discharge by Day 28 • Among patients not receiving MV, progression to MV or death by Day 28	• Proportion discharged by Day 28: 66% in both arms • Proportion who progressed to MV or death by Day 28: 29% in CCP arm vs. 29% in usual care arm	
CSSC-004: RCT of Early Treatment With High-Titer CCP in Outpatients With COVID-19 in the United States[4]		
Key Inclusion Criterion • COVID-19 symptoms for <8 days **Key Exclusion Criteria** • Prior or planned COVID-19–related hospitalization • Receipt of anti-SARS-CoV-2 mAbs **Interventions** • Approximately 250 mL of CCP with SARS-CoV-2 spike-RBD IgG titer ≥1:320 (n = 592) • Non-SARS-CoV-2 plasma (n = 589) **Primary Endpoint** • COVID-19–related hospitalization or all-cause death within 28 days	**Participant Characteristics** • Median age 44 years; 7% aged ≥65 years; 57% women; 79% White • 8% with type 2 DM; 2% with CVD; 38% with BMI ≥30 • 82% unvaccinated • Median time from symptom onset to transfusion: 6 days **Primary Outcomes** • COVID-19–related hospitalization within 28 days: 2.9% in CCP arm vs. 6.3% in control arm (absolute risk reduction 3.4 percentage points; 95% CI, 1.0–5.8; $P = 0.005$) • 53 of 54 hospitalizations occurred in unvaccinated individuals. None occurred in fully vaccinated individuals. • All-cause deaths within 28 days: 0 in CCP arm vs. 3 in control arm	**Key Limitation** • Patients were at relatively low risk for disease progression. **Interpretation** • This trial demonstrated a benefit of CCP in unvaccinated outpatients with <8 days of COVID-19 symptoms.

Methods	Results	Limitations and Interpretation
CONV-ERT: RCT of High-Titer, Methylene Blue-Treated CCP as an Early Treatment for Outpatients With COVID-19 in Spain[5]		
Key Inclusion Criteria • Aged ≥50 years • Mild or moderate COVID-19 symptoms for ≤7 days **Key Exclusion Criteria** • Severe COVID-19 symptoms or requirement for hospitalization for any reason • Previous SARS-CoV-2 infection • Receipt of ≥1 COVID-19 vaccination **Interventions** • 250–300 mL of high-titer, methylene blue-treated CCP (n = 188) • 0.9% saline (n = 188) **Primary Endpoints** • Hospitalization within 28 days • Mean change in SARS-CoV-2 VL from baseline to Day 7 **Key Secondary Endpoints** • Death by Day 60 • Time to complete symptom resolution	**Participant Characteristics** • Mean age 56 years; 54% men • 75% with ≥1 risk factor for COVID-19 progression • 97% with mild COVID-19 • Median 4.4 days of symptoms prior to enrollment • Among 369 patients with available baseline serologic testing, 88% negative for both IgG anti-SARS-CoV-2 spike and IgM anti-SARS-CoV-2 S1-RBD **Primary Outcomes** • Hospitalization within 28 days: 12% in CCP arm vs. 11% in placebo arm (relative risk 1.05; 95% CrI, 0.78–1.41) • Mean change in SARS-CoV-2 VL: -2.41 $\log_{10}$ copies/mL in CCP arm vs. -2.32 $\log_{10}$ copies/mL in placebo arm **Key Secondary Outcomes** • Death: 0 in CCP arm vs. 2 in placebo arm (relative risk 0.20; 95% CI 0.01–4.14) • No difference between arms in median time to symptom resolution: 12.0 days for both arms (HR 1.05; 95% CI, 0.85–1.30)	**Key Limitations** • Trial was underpowered because it was terminated early due to rising vaccination rates among the eligible patient population. • Methylene blue, which was used for pathogen inactivation in donor plasma, could have potentially impaired Fc-region functionality of Ig and negatively impacted product efficacy and blinding. **Interpretation** • This trial did not demonstrate a benefit of CCP in unvaccinated outpatients with <7 days of COVID-19 symptoms.
Double-Blind RCT of Early High-Titer CCP Therapy to Prevent Severe COVID-19 in Nonhospitalized Older Adults in Argentina[6]		
Key Inclusion Criteria • Aged ≥75 years or aged 65–74 years with ≥1 coexisting condition • Mild COVID-19 symptoms for <72 hours **Key Exclusion Criterion** • Severe respiratory disease **Interventions** • 250 mL of CCP with IgG against SARS-CoV-2 spike protein >1:1,000 (n = 80) • Saline (n = 80)	**Participant Characteristics** • Mean age 77 years; 38% men • Most with comorbidities **Primary Outcome** • Severe respiratory disease by Day 15: 16% in CCP arm vs. 31% in placebo arm (relative risk 0.52; 95% CI, 0.29–0.94; $P = 0.03$)	**Key Limitations** • Small sample size • Early termination because number of COVID-19 cases decreased **Interpretation** • This trial demonstrated a benefit of CCP in older adult outpatients with <72 hours of mild COVID-19 symptoms.

Methods	Results	Limitations and Interpretation
Double-Blind RCT of Early High-Titer CCP Therapy to Prevent Severe COVID-19 in Nonhospitalized Older Adults in Argentina[6]		
Primary Endpoint • Severe respiratory disease, defined as respiratory rate ≥30 breaths/min and/or SpO_2 <93% on room air by Day 15		
SIREN-C3PO: Multicenter, Single-Blind RCT of High-Titer CCP in Adults With COVID-19 in the United States[7]		
Key Inclusion Criteria • ED patient with ≤7 days of symptoms • PCR-confirmed SARS-CoV-2 infection • Aged ≥50 years or aged ≥18 years with ≥1 risk factor for disease progression **Key Exclusion Criterion** • Need for supplemental oxygen **Interventions** • 250 mL high-titer CCP (median titer 1:641) (n = 257) • Saline (n = 254) **Primary Endpoint** • Disease progression, defined as hospital admission, death, or seeking emergency or urgent care within 15 days of randomization **Key Secondary Endpoints** • Severity of illness, as measured by OS • All-cause mortality within 30 days • Number of hospital-free days by Day 30	**Participant Characteristics** • Median age 54 years; 46% men • More patients with immunosuppression in CCP arm than in placebo arm (13% vs. 7%) • More patients with ≥3 risk factors in CCP arm than in placebo arm (55% vs. 48%) **Primary Outcomes** • No difference between arms in proportion with disease progression: 30% in CCP arm vs. 32% in placebo arm (risk difference 1.9%; 95% CrI, -6.0% to 9.8%) • 25 patients (19 in CCP arm and 6 in placebo arm) required hospitalization during the index visit. In a post hoc analysis that excluded these patients, disease progression occurred in 24% in CCP arm vs. 30% in placebo arm (risk difference 5.8%; 95% CrI, -1.9% to 13.6%). **Secondary Outcomes** • All-cause mortality within 30 days: 5 (1.9%) in CCP arm vs. 1 (0.4%) in placebo arm • No difference between arms in illness severity or mean number of hospital-free days	**Key Limitations** • In the primary analysis, the number of patients who required hospital admission during the index visit was not balanced across arms. • The CCP arm included slightly more patients with multiple risk factors, including immunosuppression. **Interpretation** • The use of high-titer CCP within 1 week of symptom onset did not prevent disease progression in outpatients with COVID-19 who were at high risk of severe disease.
CoV-Early: Double-Blind RCT of CCP in Nonhospitalized High-Risk Adults With COVID-19 in the Netherlands[8]		
Key Inclusion Criteria • Aged ≥70 years, aged ≥50 years with a comorbidity, or aged ≥18 years and severely immunocompromised • Positive SARS-CoV-2 RT-PCR or antigen test result • ≤7 days of symptoms	**Participant Characteristics** • Median age 60 years; 22% women • Median 5 days of symptoms • Median 1 comorbidity • Median SpO_2 97% at baseline	**Key Limitations** • Study was discontinued after 421 of 690 planned participants were enrolled, resulting in decreased power. • The CCP used was selected based on a PRNT50 assay and may not qualify

Methods	Results	Limitations and Interpretation
CoV-Early: Double-Blind RCT of CCP in Nonhospitalized High-Risk Adults With COVID-19 in the Netherlands[8], continued		
Key Exclusion Criteria • Life expectancy <28 days • History of transfusion-related acute lung injury • IgA deficiency **Interventions** • 300 mL CCP with minimum PRNT50 titer of 1:160 (n = 207) • Non-SARS-CoV-2 plasma collected prior to pandemic (n = 209) **Primary Endpoint** • Improvement based on 5-point OS by Day 28 **Secondary Endpoints** • Percentage of hospital admissions • Number of days of symptoms	• 7.9% SARS-CoV-2 IgG antibody negative at baseline • 2.9% fully vaccinated; 5.0% received 1 vaccine **Primary Outcome** • Odds of being at highest score on 5-point OS by Day 28: OR 0.86; 95% CrI, 0.59–1.22 in CCP arm **Secondary Outcomes** • Percentage of hospital admissions: 4.8% (10 patients) in CCP arm vs. 8.6% (18 patients) in non-SARS-CoV-2 arm (aHR 0.61; 95% CI, 0.28–1.34) • Number of days of symptoms: no difference between arms (13 days in CCP arm vs. 12 days in non-CCP arm; *P* = 0.99)	as high-titer per the current FDA EUA for CCP. **Interpretation** • This trial did not demonstrate a benefit of CCP in nonhospitalized high-risk patients with COVID-19.
Retrospective Evaluation of CCP Antibody Levels and the Risk of Death From COVID-19 in the United States[9]		
Key Inclusion Criteria • Severe or life-threatening COVID-19 • Patients for whom samples of transfused CCP were available for retrospective analysis of antibody titer **Interventions** • High-titer CCP (n = 515), medium-titer CCP (n = 2,006), or low-titer CCP (n = 561), characterized retrospectively **Primary Endpoint** • Mortality at 30 days after CCP transfusion	**Participant Characteristics** • 31% aged ≥70 years; 61% men; 48% White, 37% Hispanic/Latinx • 61% in ICU; 33% on MV • 51% received corticosteroids, 31% received RDV **Primary Outcomes** • Mortality at 30 days after transfusion: 22% in high-titer CCP arm vs. 27% in medium-titer CCP arm vs. 30% in low-titer CCP arm • Lower risk of death in high-titer CCP arm than low-titer CCP arm (relative risk 0.75; 95% CI, 0.61–0.93) • Lower mortality among patients not receiving MV before CCP transfusion (relative risk 0.66; 95% CI, 0.48–0.91) • Among patients on MV before CCP transfusion, no difference in mortality between high-titer and low-titer arms (relative risk 1.02; 95% CI, 0.78–1.32)	**Key Limitation** • Lack of untreated control arm **Interpretation** • The study data are not sufficient to establish the efficacy or safety of CCP.

Key: ASAP = as soon as possible; BMI = body mass index; CCP = COVID-19 convalescent plasma; CVD = cardiovascular disease; DM = diabetes mellitus; ECMO = extracorporeal membrane oxygenation; ED = emergency department; EUA = Emergency Use Authorization; Fc = fragment crystallizable; FDA = Food and Drug Administration; HFNC = high-flow nasal cannula; ICU = intensive care unit; Ig = immunoglobulin; IL = interleukin; LOS = length of stay; mAb = monoclonal antibody; MV = mechanical ventilation; NIV = noninvasive ventilation; OS = ordinal scale; the Panel = the COVID-19 Treatment Guidelines Panel; PCR = polymerase chain reaction; PRNT50 = 50% plaque reduction neutralization test; RBD = receptor-binding domain; RCT = randomized controlled trial; RDV = remdesivir; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SOC = standard of care; SpO_2 = oxygen saturation; VL = viral load

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Interferons

Last Updated: December 16, 2021

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

Recommendations

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

Rationale

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

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

Other interferons, including systemic interferon alfa or lambda and inhaled interferons, have also been evaluated in patients with COVID-19; however, these interferons (with the exception of subcutaneous interferon alfa) are not available in the United States. The trials that have evaluated interferon alfa and interferon lambda have generally been small or moderate in size and have not been adequately powered to assess whether these agents provide a clinical benefit for patients with COVID-19 (see Table 4d).

Clinical Trials

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

Adverse Effects

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

suicidal ideation). Interferon beta is better tolerated than interferon alfa, but it can cause similar types of adverse effects.[6,7]

Drug-Drug Interactions

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

Considerations in Pregnancy

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

Considerations in Children

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

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Table 4d. Interferons: Selected Clinical Data

Last Updated: December 16, 2021

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

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

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

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

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

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

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

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

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

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

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Table 4e. Characteristics of Antiviral Agents, Including Antibody Products

Last Updated: December 1, 2022

- This table contains drugs and products that have shown antiviral activity against SARS-CoV-2, including small-molecule antiviral drugs, mAbs, CCP, and IFNs.
- RDV is the only antiviral drug that is approved by the FDA for the treatment of COVID-19.
- RTV-boosted nirmatrelvir, MOV, and CCP have received EUAs from the FDA for the treatment of COVID-19. TIX plus CIL received an EUA for SARS-CoV-2 PrEP.
- Other medications that are currently being evaluated in clinical trials for the treatment of COVID-19 are also included in this table. **The inclusion of these drugs does not imply that the Panel recommends their use.**
- For drug-drug interaction information, please refer to product labels, EUA fact sheets, and Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications.
- For the Panel's recommendations on using the drugs listed in this table, please refer to the individual drug sections, Therapeutic Management of Nonhospitalized Adults With COVID-19, Therapeutic Management of Hospitalized Adults With COVID-19, Therapeutic Management of Nonhospitalized Children With COVID-19, or Antiviral Agents, Including Antibody Products.

Drug Name	Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments
Anti-SARS-CoV-2 Antiviral Drugs (Small-Molecule Antivirals)					
Ritonavir-Boosted Nirmatrelvir (Paxlovid) *Authorized under an FDA EUA for the treatment of mild to moderate COVID-19 in high-risk individuals aged ≥12 years and weighing ≥40 kg.*	**Dose Recommended in FDA EUA**[1] *eGFR ≥60 mL/min* • Nirmatrelvir 300 mg (two 150-mg tablets) with RTV 100 mg (one 100-mg tablet) twice daily for 5 days *eGFR ≥30 to 60 mL/min* • Nirmatrelvir 150 mg (one 150-mg tablet) with RTV 100 mg (one 100-mg tablet) twice daily for 5 days *eGFR <30 mL/min* • **Not recommended** (see comments) *Severe Hepatic Impairment (Child-Pugh Class C)* • **Not recommended**	• Dysgeusia • Diarrhea • Anaphylaxis and other HSRs	• Monitor for potential AEs due to drug-drug interactions with concomitant medications. • Use with caution in patients with pre-existing liver diseases, liver enzyme abnormalities, or hepatitis. • Consider checking renal function in patients with suspected renal	• RTV-boosted nirmatrelvir has significant drug-drug interactions. Before prescribing RTV-boosted nirmatrelvir, **carefully review concomitant medications**, including OTC medicines, herbal supplements, and recreational drugs. • See Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications for	• Until more data are available, the EUA does not recommend using RTV-boosted nirmatrelvir when eGFR is <30 mL/min. See Ritonavir-Boosted Nirmatrelvir (Paxlovid) for more information. • Both nirmatrelvir and RTV tablets can be taken with or without food.

Drug Name	Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments
Anti-SARS-CoV-2 Antiviral Drugs (Small-Molecule Antivirals), continued					
			impairment. • Monitor for HSRs.	additional guidance and resources to assist with identifying drug-drug interactions.	• The EUA advises against crushing nirmatrelvir and RTV tablets. However, some data indicate that the tablets can be split or crushed if necessary.[2]
Remdesivir *Approved by the FDA for the treatment of COVID-19 in individuals aged ≥28 days and weighing ≥3 kg.*	**Dose for Adults and Children Weighing ≥40 kg** • RDV 200 mg IV on Day 1, then RDV 100 mg IV once daily from Day 2 **Dose for Children Aged ≥28 Days and Weighing 3 kg to <40 kg** • RDV 5 mg/kg IV on Day 1, then RDV 2.5 mg/kg IV once daily from Day 2 **Total Treatment Duration** *Nonhospitalized Patients* • 3 days *Hospitalized Patients* • 5 days or until hospital discharge	• Nausea • ALT and AST elevations • HSRs • Increases in prothrombin time • Drug vehicle is SBECD, which has been associated with renal and liver toxicity. SBECD may accumulate in patients with moderate or severe renal impairment. • Each 100-mg vial of RDV lyophilized powder contains 3 g of SBECD, and each 100-mg/20-mL vial of RDV solution contains 6 g of SBECD. • Consider preferentially using the lyophilized powder formulation (which contains less SBECD) in patients with renal impairment.	• Monitor patients for infusion reactions during the infusion and observe them for ≥1 hour after the infusion as clinically appropriate. • Monitor renal function, hepatic function, and prothrombin time as clinically indicated.	• Clinical drug-drug interaction studies of RDV have not been conducted. • In vitro, RDV is a minor substrate of CYP3A4; a substrate of OATP1B1 and P-gp; and an inhibitor of CYP3A4, OATP1B1, OATP1B3, and MATE1.[3]	• The FDA does not recommend using RDV when eGFR is <30 mL/min. See Remdesivir for information on using RDV in people with renal insufficiency.

Drug Name	Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments
Anti-SARS-CoV-2 Antiviral Drugs (Small-Molecule Antivirals), continued					
Molnupiravir *Authorized under an FDA EUA for the treatment of mild to moderate COVID-19 in high-risk individuals aged ≥18 years.*	**Dose Recommended in FDA EUA** • MOV 800 mg (four 200-mg capsules) PO every 12 hours for 5 days • MOV is not authorized for use in people aged <18 years due to potential effects on bone and cartilage growth.	• Diarrhea • Nausea • Dizziness • Per the FDA, the 5-day course of MOV has a low risk for genotoxicity.[4] See Molnupiravir for details.	• Before initiating MOV, assess pregnancy status as clinically indicated. • Monitor for potential AEs.	• Clinical drug-drug interaction studies of MOV have not been conducted. • Drug-drug interactions related to hepatic metabolism are not expected.	• MOV can be taken with or without food. • People of reproductive potential who are sexually active should use effective contraception during and after treatment with MOV. See Molnupiravir for details. • If MOV is prescribed for a pregnant person, the clinician should document that the risks and benefits were discussed with the patient and that the patient chose to receive MOV. Pregnant patients should also be offered the opportunity to participate in the MOV pregnancy surveillance program. • Lactating people **should not breastfeed** their infants during treatment with MOV and for 4 days after treatment.

Drug Name	Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments
Anti-SARS-CoV-2 Monoclonal Antibodies					
Tixagevimab Plus Cilgavimab (Evusheld) *Authorized under an FDA EUA for SARS-CoV-2 PrEP in adults and children aged ≥12 years and weighing ≥40 kg. See Prevention of SARS-CoV-2 Infection for eligibility criteria.*	**Dose Recommended in FDA EUA** • TIX 300 mg plus CIL 300 mg as 2 consecutive 3-mL IM injections • Individuals who received TIX 150 mg plus CIL 150 mg should receive TIX 300 mg plus CIL 300 mg as soon as possible.	• HSRs, including anaphylaxis and injection-related reactions • In 1 clinical trial, cardiac events were reported in participants with cardiac risk factors (0.6% in TIX plus CIL arm vs. 0.2% in placebo arm).[5]	• Use with caution in individuals with thrombocytopenia or any coagulation disorder. • Monitor for ≥1 hour after injections.	• If a person has received a COVID-19 vaccine, TIX plus CIL should be administered ≥2 weeks after vaccination. • Drug-drug interactions are unlikely between TIX plus CIL and medications that are renally excreted or that are CYP substrates, inhibitors, or inducers.	• Some circulating SARS-CoV-2 Omicron subvariants may have reduced susceptibility to TIX plus CIL. The Panel continues to monitor the prevalence of these subvariants and provide updated recommendations as needed.
COVID-19 Convalescent Plasma					
High-Titer COVID-19 Convalescent Plasma *Authorized under an FDA EUA for the treatment of COVID-19 in patients who are immunocompromised or who are receiving immunosuppressive treatment.*	**Dose Recommended in FDA EUA** • Consider starting clinical dosing with 1 high-titer CCP unit (about 200 mL), with administration of additional CCP units based on the prescribing provider's judgment and the patient's clinical response.	• TRALI • TACO • Allergic reactions • Anaphylactic reactions • Febrile nonhemolytic reactions • Hemolytic reactions • Hypothermia • Metabolic complications • Transfusion-transmitted infections[6] • Thrombotic events • Theoretical risk of antibody-mediated enhancement of infection and suppressed long-term immunity	• Before administering CCP to patients with a history of severe allergic or anaphylactic transfusion reactions, consult a transfusion medicine specialist who is associated with the hospital's blood bank. • Monitor for transfusion-related reactions. • Monitor vital signs at baseline and during and after transfusion.	• Drug products **should not be added** to the IV infusion line for the blood product.	• In patients with impaired cardiac function and heart failure, it may be necessary to reduce the CCP volume or decrease the transfusion rate.

Drug Name	Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments
Interferons					
IFN Beta *Not approved by the FDA and not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*	• Various doses and durations for IFN beta-1a and IFN beta-1b are being studied in clinical trials.	• Flu-like symptoms (e.g., fever, fatigue, myalgia) • Leukopenia, neutropenia, thrombocytopenia, lymphopenia • Liver function abnormalities (ALT > AST) • Injection site reactions • Headache • Hypertonia • Pain • Rash • Worsening depression • Induction of autoimmunity	• CBC with differential • Liver enzymes • Worsening CHF • Depression, suicidal ideation	• Low potential for drug-drug interactions • **Use with caution** with other hepatotoxic agents. • Reduce dose if ALT is >5 times ULN.	**Availability** *Brand Names of IFN Beta-1a Products* • Avonex, Plegridy, Rebif • Inhaled IFN beta-1a is not approved by the FDA for use in the United States. *Brand Names of IFN Beta-1b Products* • Betaseron, Extavia

Key: AE = adverse event; ALT = alanine transaminase; AST = aspartate aminotransferase; CBC = complete blood count; CCP = COVID-19 convalescent plasma; CHF = congestive heart failure; CIL = cilgavimab; CYP = cytochrome P450; eGFR = estimated glomerular filtration rate; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; HSR = hypersensitivity reaction; IFN = interferon; IM = intramuscular; IV = intravenous; mAb = monoclonal antibody; MATE = multidrug and toxin extrusion protein; MOV = molnupiravir; OATP = organic anion transporting polypeptide; OTC = over-the-counter; the Panel = the COVID-19 Treatment Guidelines Panel; P-gp = P-glycoprotein; PO = orally; PrEP = pre-exposure prophylaxis; RDV = remdesivir; RTV = ritonavir; SBECD = sulfobutylether-beta-cyclodextrin; TACO = transfusion-associated circulatory overload; TIX = tixagevimab; TRALI = transfusion-related acute lung injury; ULN = upper limit of normal

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Immunomodulators

Last Updated: December 1, 2022

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 and Therapeutic Management of Hospitalized Children With COVID-19 for the COVID-19 Treatment Guidelines Panel's (the Panel) recommendations on the use of the following immunomodulators for hospitalized patients according to their disease severity: • *Corticosteroids:* Dexamethasone • *Interleukin-6 inhibitors:* Tocilizumab (or sarilumab) • *Janus kinase (JAK) inhibitors:* Baricitinib (or tofacitinib) There is insufficient evidence for the Panel to recommend either for or against the use of the following immunomodulators for the treatment of COVID-19: • Anakinra • Granulocyte-macrophage colony-stimulating factor inhibitors in hospitalized patients • Inhaled corticosteroids The Panel **recommends against** the use of the following immunomodulators for the treatment of COVID-19, except in a clinical trial: • **Canakinumab (BIIa)** • **Bruton's tyrosine kinase inhibitors** (e.g., **acalabrutinib**, **ibrutinib**, **zanubrutinib**) **(AIII)** • **JAK inhibitors other than baricitinib and tofacitinib** (e.g., **ruxolitinib**) **(AIII)** • **Siltuximab (BIII)**
Each recommendation in the Guidelines receives 2 ratings that reflect the strength of the recommendation and the quality of the evidence that supports it. See Guidelines Development for more information.

Corticosteroids

Last Updated: May 31, 2022

Multiple randomized trials indicate that systemic corticosteroid therapy improves clinical outcomes and reduces mortality in hospitalized patients with COVID-19 who require supplemental oxygen,[1,2] presumably by mitigating the COVID-19-induced systemic inflammatory response that can lead to lung injury and multisystem organ dysfunction. In contrast, in hospitalized patients with COVID-19 who do not require supplemental oxygen, the use of systemic corticosteroids has not shown any benefits and may cause harm.[3,4] The COVID-19 Treatment Guidelines Panel's (the Panel) recommendations for the use of corticosteroids in hospitalized patients with COVID-19 are based on results from these clinical trials (see Tables 5a and 5b for more information). There are no data to support the use of systemic corticosteroids in nonhospitalized patients with COVID-19.

Recommendations

For Nonhospitalized Adults With COVID-19

- See Therapeutic Management of Nonhospitalized Adults With COVID-19 for the Panel's recommendations on the use of dexamethasone or other systemic corticosteroids in certain nonhospitalized patients.
- There is insufficient evidence for the Panel to recommend either for or against the use of inhaled corticosteroids for the treatment of COVID-19 in these patients.
- Patients with COVID-19 who are receiving **dexamethasone** or **another corticosteroid** for an underlying condition should continue this therapy as directed by their health care provider **(AIII)**.

For Hospitalized Adults With COVID-19

- See Therapeutic Management of Hospitalized Adults With COVID-19 for the Panel's recommendations on the use of dexamethasone or other systemic corticosteroids in certain hospitalized patients.
- There is insufficient evidence for the Panel to recommend either for or against the use of inhaled corticosteroids for the treatment of COVID-19 in these patients.

Systemic Corticosteroids in Patients With COVID-19

Nonhospitalized Adults

There are no data to support the use of systemic corticosteroids in nonhospitalized patients with COVID-19. Therefore, the safety and efficacy of using systemic corticosteroids in this population have not been established. Generally, the use of systemic corticosteroids is associated with adverse events (e.g., hyperglycemia, neuropsychiatric symptoms, secondary infections), which may be difficult to detect and monitor in an outpatient setting. For more information, see General Management of Nonhospitalized Adults With Acute COVID-19.

Hospitalized Adults

The RECOVERY trial was a multicenter, open-label trial in the United Kingdom that randomly assigned 6,425 hospitalized patients to receive up to 10 days of dexamethasone 6 mg once daily plus standard care or standard care alone. Mortality at 28 days was lower among the patients who received

dexamethasone than among those who received standard care alone.[3] This benefit of dexamethasone was observed in patients who were mechanically ventilated or who required supplemental oxygen at enrollment; in contrast, no benefit was seen in patients who did not require supplemental oxygen at enrollment.[3]

The CoDEX trial was a multicenter, open-label trial in Brazil that evaluated dexamethasone in patients who were mechanically ventilated due to acute respiratory distress syndrome (ARDS) induced by COVID-19. Although the trial was terminated early, the study results support the RECOVERY trial finding that systemic corticosteroids are beneficial in hospitalized patients with COVID-19. The trial randomly assigned 299 patients to receive either standard care plus intravenous (IV) dexamethasone 20 mg once daily for 5 days and then dexamethasone 10 mg IV once daily for 5 days or standard care alone. The mean number of days alive and free from mechanical ventilation over 28 days was greater in the dexamethasone arm than in the standard care alone arm. However, there were no differences between the arms in 28-day mortality, the mean number of intensive care unit-free days at 28 days, or the mean duration of mechanical ventilation at 28 days.[5]

An observational study evaluated the use of corticosteroids in 15,404 hospitalized patients with positive SARS-CoV-2 polymerase chain reaction results or antigen test results from the Department of Veteran Affairs' database.[4] Corticosteroids were administered to 60% of the patients within 48 hours of admission, and 95% of the patients who received corticosteroids received dexamethasone. A total of 9,450 patients did not receive supplemental oxygen during the study. Of these patients, 3,514 (37%) received dexamethasone, administered for a median duration of 5 days (IQR 3–8 days). Using average treatment effect estimates, patients who received dexamethasone without supplemental oxygen had an increased risk of death within 90 days (HR 1.76; 95% CI, 1.47–2.12). Patients who received dexamethasone either without supplemental oxygen or with low-flow nasal cannula oxygen had a 60% higher risk of death. Although this study was observational, the investigators employed several statistical techniques to minimize potential bias, including propensity scoring and weighted analyses. Additionally, several subgroup and sensitivity analyses in this study confirmed the overall results.

Dose of Dexamethasone

The COVID STEROID 2 trial is the largest study to date that has investigated the use of different doses of corticosteroids in people with COVID-19.[6] This multicenter trial randomized hospitalized patients to receive up to 10 days of once-daily dexamethasone 6 mg (n = 485) or dexamethasone 12 mg (n = 497). The median number of days alive without life support at 28 days after randomization was 20.5 days in the dexamethasone 6 mg arm (IQR 4.0–28.0 days) and 22.0 days in the dexamethasone 12 mg arm (IQR 6.0–28.0 days), yielding an adjusted mean difference of 1.3 days (95% CI, 0–2.6; $P = 0.07$). No differences were found in 28- or 90-day mortality between the arms. Approximately 12% of the patients in each arm received either an interleukin-6 inhibitor or a kinase inhibitor during the study. While these conventional analyses did not reach statistical significance, a preplanned Bayesian analysis found a higher probability of benefit and a lower probability of harm for the 12-mg dose than for the 6-mg dose.[7]

A smaller randomized controlled trial reported a shorter time to clinical improvement and a lower frequency of adverse events in patients with COVID-19 who received a lower dose of dexamethasone (8 mg IV once daily) compared to those who received higher doses (8 mg IV 2 or 3 times daily). A lower proportion of patients in the low-dose group died within 60 days compared to the intermediate- and high-dose groups (17% vs. 30% and 41%, respectively; $P = 0.06$). It is worth noting that this study included <200 participants.[8]

A third small, open-label, randomized trial (with <100 participants) found no difference in the median number of ventilator-free days at 28 days after randomization between patients who received higher

doses of dexamethasone (16 mg IV daily for 5 days, followed by 8 mg daily for 5 days) and those who received lower doses (6 mg IV daily for 10 days).[9]

The mixed results from these studies have led the Panel to continue to recommend 6 mg once daily as the preferred dose for dexamethasone. However, the Panel notes that both the traditional and Bayesian analyses conducted during the COVID STEROID 2 trial suggest that the 12-mg dose might confer a benefit in patients who require high levels of respiratory support. As a result, some clinicians might choose to use the higher dose of dexamethasone in these patients. It should be noted that there are currently no data evaluating the safety and efficacy of using lower or higher doses of corticosteroids in combination with other immunomodulators to treat COVID-19.

Combination Immunomodulator Therapy

Using systemic corticosteroids in combination with other agents, including tocilizumab (see Interleukin-6 Inhibitors)[10,11] or baricitinib (see Kinase Inhibitors),[12] has been shown to have a clinical benefit in subsets of hospitalized patients with COVID-19, especially those with early critical illness and/or those with signs of systemic inflammation. For the Panel's recommendations on when to use dexamethasone with another immunomodulator, see Therapeutic Management of Hospitalized Adults With COVID-19.

Please see Tables 5a and 5b for data from clinical trials that have evaluated the use of corticosteroids in patients with COVID-19.

Systemic Corticosteroids Other Than Dexamethasone

Systemic corticosteroids other than dexamethasone, including hydrocortisone[13,14] and methylprednisolone,[15,16] have been studied for the treatment of COVID-19 in several randomized trials. Some of these trials were stopped early due to under-enrollment following the release of the RECOVERY trial results. Consequently, the sample size of many these trials was insufficient to assess efficacy (i.e., there were too few events to definitively confirm or exclude an effect, although many point estimates suggested a beneficial effect). Therefore, the evidence supporting the use of hydrocortisone or methylprednisolone for the treatment of COVID-19 is not as strong as the evidence supporting the use of dexamethasone. Based on the available evidence, the Panel has concluded the following:

- If dexamethasone is not available, alternative glucocorticoids (e.g., prednisone, methylprednisolone, hydrocortisone) can be used.
- For these drugs, the total daily dose equivalencies to dexamethasone 6 mg (orally or IV)[17] are:
  - Prednisone 40 mg
  - Methylprednisolone 32 mg
  - Hydrocortisone 160 mg
- Half-life, duration of action, and frequency of administration vary among corticosteroids.
  - *Long-acting corticosteroid:* Dexamethasone; half-life 36 to 72 hours, administer once daily.
  - *Intermediate-acting corticosteroids:* Prednisone and methylprednisolone; half-life 12 to 36 hours, administer once daily or in 2 divided doses daily.
  - *Short-acting corticosteroid:* Hydrocortisone; half-life 8 to 12 hours, administer in 2 to 4 divided doses daily.
- Hydrocortisone is commonly used to manage septic shock in patients with COVID-19; see Hemodynamics for more information. Unlike other corticosteroids that have previously been

studied in patients with ARDS, dexamethasone lacks mineralocorticoid activity and thus its effects on sodium balance and fluid volume are minimal.[18]

Inhaled Corticosteroids in Patients With COVID-19

Inhaled corticosteroids have been identified as potential COVID-19 therapeutic agents because of their targeted anti-inflammatory effects on the lungs. In addition, certain inhaled corticosteroids have been shown to impair viral replication of SARS-CoV-2[19] and downregulate the expression of the receptors used for cell entry.[20,21] Two open-label randomized controlled trials and 2 double-blind, placebo-controlled trials provide additional insights regarding the role of inhaled corticosteroids in outpatients with COVID-19, as described below and in Table 5b.

Recommendation

- There is insufficient evidence for the Panel to recommend either for or against the use of inhaled corticosteroids for the treatment of COVID-19.

Rationale

Inhaled budesonide was studied in 2 open-label randomized controlled trials in outpatients with mild symptoms of COVID-19.[22,23] The small STOIC trial suggested that initiating inhaled budesonide in adult outpatients with mild COVID-19 may reduce the need for urgent care or emergency department assessment or hospitalization.[22] PRINCIPLE, a larger, open-label trial in nonhospitalized patients with COVID-19 who were at high risk of disease progression, found that using inhaled budesonide did not affect the rate of hospitalization or death but did reduce the time to self-reported recovery.[23] The findings from these trials should be interpreted with caution given the open-label design of the studies and other limitations.

Inhaled ciclesonide was studied in 2 double-blind, randomized, placebo-controlled trials in outpatients with mild COVID-19. The primary endpoint in 1 study was time to alleviation of COVID-19-related symptoms. In this study, the use of inhaled ciclesonide did not reduce the time to self-reported recovery, but the therapy did reduce the number of subsequent COVID-related emergency department visits or hospitalizations. The robustness of this conclusion is uncertain given the small number of events, which is likely due to the relatively small number of participants with comorbidities.[24] In the smaller CONTAIN study, the combined use of inhaled and intranasal ciclesonide did not improve the resolution of fever and/or respiratory symptoms by Day 7.[25]

The studies described above that evaluated the use of inhaled corticosteroid therapy in outpatients with mild COVID-19 have identified inconsistent effects of this therapy on subsequent hospitalization, and similar placebo-controlled trials have not demonstrated that this therapy improves the time to symptom resolution. The placebo-controlled studies did not enroll enough patients who were at high risk of disease progression; therefore, further studies in this population are needed. For additional information on these trials, see Table 5b.

Monitoring, Adverse Effects, and Drug-Drug Interactions

- Clinicians should closely monitor patients with COVID-19 who are receiving dexamethasone for certain adverse effects (e.g., hyperglycemia, secondary infections, psychiatric effects, avascular necrosis).
- Patients who are receiving inhaled corticosteroids may develop oral candidiasis.
- The use of systemic corticosteroids may increase the risk of opportunistic fungal infections (e.g., mucormycosis, aspergillosis) and reactivation of latent infections (e.g., hepatitis B virus infection,

herpesvirus infections, strongyloidiasis, tuberculosis).[26-30]

- Cases of severe and disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with tocilizumab and corticosteroids.[31,32] Many clinicians would initiate empiric antiparasitic treatment (e.g., with the antiparasitic drug ivermectin) with or without serologic testing in patients who currently reside or who have previously resided in areas where *Strongyloides* is endemic (i.e., tropical, subtropical, or warm temperate areas).[33]
- Using systemic corticosteroids with other immunosuppressants, such as tocilizumab or baricitinib, could theoretically increase the risk of secondary infections. However, clinical trials have reported no difference in the rates of secondary infections between patients who received corticosteroids in combination with another immunomodulatory agent and those who received corticosteroids alone.
- Dexamethasone is a moderate cytochrome P450 (CYP) 3A4 inducer. Therefore, it could reduce the concentration and potential efficacy of concomitant medications that are CYP3A4 substrates. Clinicians should carefully review a patient's concomitant medications to assess the potential for drug-drug interactions.
- Using a CYP3A4 inhibitor with inhaled budesonide may lead to increased systemic absorption of budesonide, which may result in systemic adverse effects from the corticosteroid.

Considerations in Pregnancy

A short course of betamethasone or dexamethasone, which are both known to cross the placenta, is routinely used to decrease neonatal complications of prematurity in women with threatened preterm delivery.[34,35]

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

Considerations in Children

The safety and effectiveness of using dexamethasone or other corticosteroids for COVID-19 treatment have not been sufficiently evaluated in pediatric patients. Caution is warranted when using data from clinical trials that enrolled adults to inform treatment recommendations for children, particularly younger children and those who are less severely ill. The Panel recommends using **dexamethasone** for children with COVID-19 who require high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation **(BIII)**. Corticosteroids are not routinely recommended for pediatric patients who require only low levels of oxygen support (i.e., administered via a nasal cannula only) but could be considered on a case-by-case basis. The use of dexamethasone for the treatment of severe COVID-19 in children who are profoundly immunocompromised has not been evaluated and may be harmful; therefore, such use should be considered only if the benefit is expected to outweigh the risks. The dexamethasone dosing regimen for pediatric patients is dexamethasone 0.15 mg/kg per dose (with a maximum dose of 6 mg) once daily for up to 10 days. There is insufficient evidence to recommend either for or against the use of inhaled corticosteroids in pediatric patients with COVID-19.

Methylprednisolone or **another corticosteroid** should be used in combination with IV immunoglobulin for the initial treatment of multisystem inflammatory syndrome in children (MIS-C) **(AIIb)**. The dosing regimen for initial therapy is methylprednisolone 1 to 2 mg/kg IV once daily or another glucocorticoid at an equivalent dose. See Therapeutic Management of Hospitalized Pediatric Patients With Multisystem Inflammatory Syndrome in Children (MIS-C) (With Discussion on Multisystem Inflammatory

Syndrome in Adults [MIS-A]) for more information on the management of MIS-C.

Clinical Trials

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

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Table 5a. Systemic Corticosteroids: Selected Clinical Data

Last Updated: May 31, 2022

The clinical trials described in this table do not represent all the trials that the Panel reviewed while developing the recommendations for systemic corticosteroids. The studies summarized below are those that have had the greatest impact on the Panel's recommendations. Unless stated otherwise, the clinical trials listed below only included participants aged ≥18 years.

Methods	Results	Limitations and Interpretation
RECOVERY: Open-Label RCT of Dexamethasone in Hospitalized Patients With COVID-19 in the United Kingdom[1]		

Key Inclusion Criterion
• Hospitalized with suspected or laboratory-confirmed SARS-CoV-2 infection
Key Exclusion Criteria
• Physician determination that risks of participation were too great based on patient's medical history
• An indication for corticosteroid therapy outside of the study
Interventions
• DEX 6 mg IV or PO once daily plus SOC for up to 10 days or until discharge (n = 2,104)
• SOC alone (n = 4,321)
Primary Endpoint
• All-cause mortality at 28 days
	Participant Characteristics
	• Mean age 66 years; 64% men; 73% White
	• 56% had ≥1 comorbidity; 24% with DM
	• 89% had laboratory-confirmed SARS-CoV-2 infection
	• Median duration of DEX therapy: 7 days
	• At randomization:
	  • 16% received MV or ECMO
	  • 60% required supplemental oxygen but not MV
	  • 24% required no supplemental oxygen
	• Received RDV: <1% in both arms
	• Received tocilizumab or sarilumab: 2% in DEX arm vs. 3% in SOC arm
	Primary Outcome
	• All-cause mortality at 28 days:
	  • All patients: 23% in DEX arm vs. 26% in SOC arm (age-adjusted rate ratio 0.83; 95% CI, 0.75–0.93; $P < 0.001$)
	  • Patients who required MV or ECMO at randomization: 29% in DEX arm vs. 41% in SOC arm (rate ratio 0.64; 95% CI, 0.51–0.81)
	  • Patients who required supplemental oxygen but not MV at randomization: 23% in DEX arm vs. 26% in SOC arm (rate ratio 0.82; 95% CI, 0.72–0.94)
	  • Patients who did not require supplemental oxygen at
		Key Limitations
		• Open-label study
		• Published data did not include results for key secondary endpoints (e.g., cause-specific mortality, need for renal replacement), AEs, and key subgroups (e.g., patients with comorbidities).
		• Patients who required supplemental oxygen (but not MV) had variable severity of illness. It is unclear whether all patients in this group benefited from DEX or whether benefit is restricted to those requiring higher levels of supplemental oxygen.
		• Patients aged >80 years were preferentially assigned to receive supplemental oxygen therapy (and not MV).
		• High mortality in this study may limit the generalizability of results to populations with a lower baseline mortality.
		Interpretation
		• In hospitalized patients with severe COVID-19 who required supplemental oxygen, DEX reduced mortality at 28 days. The greatest benefit was seen in those receiving MV at randomization.
		• There was no survival benefit for DEX in patients who did not require supplemental oxygen at randomization.

Methods	Results	Limitations and Interpretation
RECOVERY: Open-Label RCT of Dexamethasone in Hospitalized Patients With COVID-19 in the United Kingdom[1], continued		
	randomization: 18% in DEX arm vs. 14% in SOC arm (rate ratio 1.19, 95% CI, 0.92–1.55)	
CoDEX: Open-Label RCT of Dexamethasone in Patients With Moderate or Severe ARDS and COVID-19 in Brazil[2]		

Key Inclusion Criteria
• Confirmed or suspected SARS-CoV-2 infection
• Received MV within 48 hours of meeting criteria for moderate to severe ARDS (PaO_2/FiO_2 ≤200 mm Hg)
Key Exclusion Criteria
• Received immunosuppressive drugs in past 21 days
• Death expected within 24 hours
Interventions
• DEX 20 mg IV once daily for 5 days, then DEX 10 mg IV once daily for 5 days or until ICU discharge (n = 151)
• SOC alone (n = 148)
Primary Endpoint
• Number of days alive and free from MV by Day 28
Key Secondary Endpoints
• All-cause mortality by Day 28
• Number of ICU-free days by Day 28
• Duration of MV by Day 28
• Score on 6-point OS at Day 15
• SOFA score at Day 7
	Participant Characteristics
	• Mean age 61 years; 63% men
	• Comorbidities:
	  • Obesity: 31% in DEX arm vs. 24% in SOC arm
	  • DM: 38% in DEX arm vs. 47% in SOC arm
	• Vasopressor use: 66% in DEX arm vs. 68% in SOC arm
	• Mean PaO_2/FiO_2: 131 mm Hg in DEX arm vs. 133 mm Hg in SOC arm
	• Median duration of DEX therapy: 10 days
	• No patients received RDV or tocilizumab
	• 35% in SOC arm received corticosteroids for indications such as bronchospasm or septic shock
	Primary Outcome
	• Mean number of days alive and free from MV by Day 28: 7 in DEX arm vs. 4 in SOC arm ($P = 0.04$)
	Secondary Outcomes
	• No differences between arms in all-cause mortality (56% vs. 62%), number of ICU-free days, duration of MV, or score on 6-point OS
	• Mean SOFA score at Day 7: 6.1 in DEX arm vs. 7.5 in SOC arm ($P = 0.004$)
	Other Outcome
	• Post hoc analysis of probability of death or MV by Day 15: 68% in DEX arm vs. 80% in SOC arm (OR 0.46)
		Key Limitations
		• Open-label study
		• Underpowered; enrollment stopped after release of data from the RECOVERY trial.
		• Patients discharged before 28 days were not followed for rehospitalization or mortality.
		• High mortality in this study may limit the generalizability of results to populations with a lower baseline mortality.
		• More than one-third of those randomized to receive SOC also received corticosteroids.
		Interpretation
		• Compared with SOC alone, DEX increased the number of days alive and free of MV over 28 days in patients with COVID-19 and moderate to severe ARDS.

Methods	Results	Limitations and Interpretation
Observational Cohort Study of Dexamethasone in Hospitalized Patients With COVID-19 Who Were Not on Intensive Respiratory Support in the United States[3]		

Key Inclusion Criterion
• Within 14 days of a positive test result for SARS-CoV-2 infection
Key Exclusion Criteria
• Recent receipt of corticosteroids
• Receipt of IRS (defined as HFNC oxygen, NIV, or MV) within 48 hours
• Hospital LOS of <48 hours
Interventions
• Corticosteroids (95% of patients received DEX) administered within 48 hours of admission (n = 7,507)
• No corticosteroids administered (n = 7,433)
Primary Endpoint
• All-cause mortality at 90 days
	Participant Characteristics
	• Mean age 71 years; 95% men; 27% Black, 55% White
	• 77% did not receive IRS within 48 hours
	• 83% admitted within 1 day after positive SARS-CoV-2 test result
	• Median duration of DEX for patients who did not receive IRS: 5 days for patients who were not on supplemental oxygen at baseline vs. 6 days for patients on low-flow nasal cannula oxygen
	• Received RDV: 43% of those who received DEX vs. 13% of those who did not
	• Received anticoagulants: 46% of those who received DEX vs. 10% of those who did not
	Primary Outcome
	• Risk of all-cause mortality at 90 days was higher in those who received DEX:
	  • For combination of those not on supplemental oxygen and those on low-flow nasal cannula oxygen: HR 1.59; 95% CI, 1.39–1.81
	  • For those not on supplemental oxygen: HR 1.76; 95% CI, 1.47–2.12
	  • For those on low-flow nasal cannula oxygen: HR 1.08; 95% CI, 0.86–1.36
		Key Limitations
		• Retrospective observational study
		• Because nearly all patients on MV or HFNC oxygen received DEX, analysis was restricted to patients who did not receive IRS (i.e., those who received no supplemental oxygen or only low-flow nasal cannula oxygen).
		• Differences between the arms in other therapies received
		Interpretation
		• In hospitalized patients with COVID-19, the use of DEX was not associated with a mortality benefit among those who received low-flow nasal cannula oxygen during the first 48 hours after admission, but it was associated with increased mortality among those who received no supplemental oxygen during the first 48 hours after admission.

Methods	Results	Limitations and Interpretation
COVID STEROID 2: Blinded RCT of Dexamethasone 12 mg Versus 6 mg in Hospitalized Adults With COVID-19 and Severe Hypoxemia in Denmark, India, Sweden, and Switzerland[4,5]		

Key Inclusion Criteria
• Confirmed SARS-CoV-2 infection
• Requiring oxygen ≥10 L/min, NIV, CPAP, or MV
Key Exclusion Criteria
• Treated with DEX >6 mg (or equivalent)
• Treated with a corticosteroid within past 5 days
• Invasive fungal infection or active TB
Interventions
• DEX 12 mg IV once daily for up to 10 days (n = 497)
• DEX 6 mg IV once daily for up to 10 days (n = 485)
Primary Endpoint
• Number of days alive without life support (MV, circulatory support, or kidney replacement therapy) at 28 days
Key Secondary Endpoints
• Number of days alive without life support at 90 days
• Number of days alive and out of hospital at 90 days
• Mortality at 90 days
• Mortality at 28 days
• SAEs at 28 days
	Participant Characteristics
	• Median age 65 years; 31% women
	• DM: 27% in 12 mg arm vs. 34% in 6 mg arm
	• Median time from symptom onset to hospitalization: 7 days in both arms
	• Received ICU care: 78% in 12 mg arm vs. 81% in 6 mg arm
	• Oxygen requirements:
	  • 54% on oxygen via nasal cannula or face mask (median flow rate 23 L/min)
	  • 25% on NIV
	  • 21% on MV
	• 63% received RDV; 12% received IL-6 inhibitors or JAK inhibitors
	• Median duration of DEX treatment: 7 days in both arms
	Primary Outcome
	• Median number of days alive without life support: 22.0 in 12 mg arm vs. 20.5 in 6 mg arm (adjusted mean difference 1.3 days; 95% CI, 0.0–2.6; $P = 0.07$)
	  • 63.9% Bayesian probability of clinically important benefit and 0.3% Bayesian probability of clinically important harm for DEX 12 mg
	Secondary Outcomes
	• At 90 days:
	  • Median number of days alive without life support: 84 in 12 mg arm vs. 80 in 6 mg arm ($P = 0.15$)
	  • Median number of days alive and out of hospital: 62 in 12 mg arm vs. 48 in 6 mg arm ($P = 0.09$)
	  • Mortality: 32% in 12 mg arm vs. 38% in 6 mg arm (adjusted relative risk 0.87; 99% CI, 0.70–1.07; $P = 0.09$)
		Key Limitation
		• The randomized intervention period was <10 days in some patients because the trial allowed up to 4 days of DEX before enrollment.
		Interpretation
		• Among patients with COVID-19 and severe hypoxemia, the use of DEX 12 mg once daily did not result in more days alive without life support at 28 days than DEX 6 mg once daily.

Methods	Results	Limitations and Interpretation
COVID STEROID 2: Blinded RCT of Dexamethasone 12 mg Versus 6 mg in Hospitalized Adults With COVID-19 and Severe Hypoxemia in Denmark, India, Sweden, and Switzerland[4,5], continued		

	• At 28 days:
	  • Mortality: 27% in 12 mg arm vs. 32% in 6 mg arm (adjusted relative risk 0.86; 99% CI, 0.68–1.08; $P = 0.10$)
	  • SAEs, including septic shock and invasive fungal infections: 11% in 12 mg arm vs. 13% in 6 mg arm (adjusted relative risk 0.83; 99% CI, 0.54–1.29; $P = 0.27$)	

CAPE COVID: Double-Blind RCT of Hydrocortisone Among Critically Ill Patients With COVID-19 in France[6]		

Key Inclusion Criteria
• Laboratory-confirmed SARS-CoV-2 infection or radiographically suspected COVID-19 with ≥1 of the following:
  • MV with PEEP ≥5 cm H_2O
  • PaO_2/FiO_2 <300 mm Hg and FiO_2 ≥50% on HFNC
  • PaO_2/FiO_2 <300 mm Hg on reservoir mask oxygen
  • Pulmonary severity index >130
Key Exclusion Criteria
• Septic shock
• Do-not-intubate orders
Interventions
• Continuous IV infusion of hydrocortisone 200 mg per day for 7 days, then 100 mg per day for 4 days, then 50 mg per day for 3 days. If patient improved by Day 4, then IV infusion of hydrocortisone 200 mg per day for 4 days, then 100 mg per day for 2 days, then 50 mg per day for 2 days (n = 76)
• Placebo (n = 73)
	Participant Characteristics
	• Mean age 62 years; 70% men; median BMI 28
	• 96% had laboratory-confirmed SARS-CoV-2 infection
	• Median symptom duration: 9–10 days
	• Required MV at baseline: 81%
	• Received vasopressors: 24% in hydrocortisone arm vs. 18% in placebo arm
	• Received RDV or tocilizumab: <5%
	• Median duration of treatment with study drug: 11 days in hydrocortisone arm vs. 13 days in placebo arm ($P = 0.25$)
	Primary Outcome
	• Treatment failure by Day 21: 42% in hydrocortisone arm vs. 51% in placebo arm ($P = 0.29$)
	Secondary Outcomes
	• No difference between arms in need for intubation or prone positioning (too few patients received ECMO or inhaled nitric oxide for comparisons)
	• Among patients who did not require MV at baseline, 50% in hydrocortisone arm vs. 75% in placebo arm required subsequent MV
	• No difference between arms in proportion of patients with nosocomial infection by Day 28
		Key Limitations
		• Underpowered; enrollment stopped after release of data from the RECOVERY trial, resulting in limited power to detect differences between arms.
		• Limited information about comorbidities
		Interpretation
		• The use of hydrocortisone did not reduce the proportion of patients with COVID-19 and acute respiratory failure who experienced treatment failure by Day 21.

Methods	Results	Limitations and Interpretation
CAPE COVID: Double-Blind RCT of Hydrocortisone Among Critically Ill Patients With COVID-19 in France[6], continued		

Primary Endpoint
• Treatment failure (death or dependency on MV or high-flow oxygen) by Day 21
Key Secondary Endpoints
• Need for MV, prone positioning, ECMO, or inhaled nitric oxide
• Nosocomial infection by Day 28
• Clinical status on Day 21, as measured by a 5-item scale:
  • Death
  • In ICU and on MV
  • Required high-flow oxygen therapy
  • Required low-flow oxygen therapy
  • Discharged from ICU
	• No difference between arms in clinical status on Day 21, but 15% died in hydrocortisone arm vs. 27% in placebo arm (P = 0.06)
	• Discharged from ICU by Day 21: 57% in hydrocortisone arm vs. 44% in placebo arm; 23% in both arms still required MV	

REMAP-CAP: Randomized, Open-Label, Adaptive Trial of Hydrocortisone in Patients With Severe COVID-19[7]		

Key Inclusion Criteria
• Presumed or laboratory-confirmed SARS-CoV-2 infection
• ICU admission for respiratory or cardiovascular support
Key Exclusion Criteria
• Presumed imminent death
• Systemic corticosteroid use
• >36 hours since ICU admission
Interventions
• Hydrocortisone 50 mg IV every 6 hours for 7 days (n = 137)
• Shock-dependent hydrocortisone 50 mg IV every 6 hours for duration of shock for up to 28 days (n = 146)
• No hydrocortisone (n = 101)
	Participant Characteristics
	• Mean age 60 years; 71% men; 53% White
	• Mean BMI 29.7–30.9
	• 50% to 64% required MV
	Primary Outcome
	• No difference between arms in median number of organ support-free days at Day 21 (0 in each arm)
	• Median adjusted ORs for primary outcome for hydrocortisone arms compared to no hydrocortisone arm:
	  • OR 1.43 (95% CrI, 0.91–2.27) with 93% Bayesian probability of superiority for fixed-dose hydrocortisone arm
	  • OR 1.22 (95% CrI, 0.76–1.94) with 80% Bayesian probability of superiority for shock-dependent hydrocortisone arm
	Key Secondary Outcome
	• No difference between arms in in-hospital mortality (30% in
		Key Limitations
		• Open-label study
		• Enrollment stopped after release of data from the RECOVERY trial.
		Interpretation
		• The use of hydrocortisone did not increase the median number of support-free days in either the fixed-dose or the shock-dependent hydrocortisone arms, although early termination limited the study's power to detect differences between the study arms.

Methods	Results	Limitations and Interpretation
REMAP-CAP: Randomized, Open-Label, Adaptive Trial of Hydrocortisone in Patients With Severe COVID-19[7], continued		
Primary Endpoint • Number of days free from respiratory and cardiovascular support by Day 21 **Key Secondary Endpoint** • In-hospital mortality	fixed-dose hydrocortisone arm vs. 26% in shock-dependent hydrocortisone arm vs. 33% in no hydrocortisone arm)	
Single-Blind RCT of Methylprednisolone in Hospitalized Patients With COVID-19 Pneumonia in China[8]		

Key Inclusion Criteria
• Laboratory-confirmed SARS-CoV-2 infection
• Pneumonia confirmed by chest CT scan
• Hospitalized on general ward for <72 hours
Key Exclusion Criteria
• Severe immunosuppression
• Corticosteroid use for other diseases
Interventions
• Methylprednisolone 1 mg/kg per day IV for 7 days (n = 43)
• Saline (n = 43)
Primary Endpoint
• Clinical deterioration at 14 days
Key Secondary Endpoints
• Clinical cure at 14 days
• Time to clinical cure
• ICU admission
• In-hospital mortality
• Number of days hospitalized
	Participant Characteristics
	• Mean age 56 years; 48% men
	• Median time from symptom onset to randomization: 8 days
	• At randomization, 71% were receiving oxygen via nasal cannula
	Primary Outcome
	• Clinical deterioration at 14 days: 4.8% in both arms (OR 1.0; 95% CI, 0.134–7.442; $P = 1.00$)
	Secondary Outcomes
	• No differences (all $P > 0.05$) between methylprednisolone arm and placebo arm for:
	  • Clinical cure at 14 days: 51% vs. 58%
	  • Median number of days to clinical cure: 14 vs. 12
	  • ICU admission: 4.8% in both arms
	  • In-hospital mortality: 0% vs. 2.3%
	  • Median number of days hospitalized: 17 vs. 13
		Key Limitations
		• Small sample size
		• Terminated early because of decreasing incidence of COVID-19 pneumonia at study sites
		Interpretation
		• The incidence of clinical deterioration did not differ between the methylprednisolone and placebo arms.

Methods	Results	Limitations and Interpretation
Single-Blind RCT of 3 Doses of Dexamethasone in Hospitalized Patients With Moderate to Severe COVID-19 in Iran[9]		
Key Inclusion Criteria • PCR-confirmed SARS-CoV-2 infection or CT scan showing lung involvement • Moderate or severe COVID-19 • Requirement for supplemental oxygen **Key Exclusion Criteria** • Uncontrolled DM • Active fungal or parasitic infection • On MV or receiving vasopressor therapy **Interventions** • Low dose: DEX 8 mg IV once daily for up to 10 days (n = 47) • Intermediate dose: DEX 8 mg IV twice daily for up to 10 days (n = 40) • High dose: DEX 8 mg IV 3 times a day for up to 10 days (n = 46) **Primary Endpoint** • Time to clinical response, as measured by OS **Key Secondary Endpoints** • Mortality at 60 days • Occurrence of AEs	**Participant Characteristics** • Mean age: 59 years in low-dose arm vs. 59 years in intermediate-dose arm vs. 56 years in high-dose arm • 50% men • 23% with DM • 75% received RDV **Primary Outcome** • Mean number of days to clinical response: 4.3 in low-dose arm vs. 5.3 in intermediate-dose arm vs. 6.1 in high-dose arm ($P = 0.025$) **Secondary Outcomes** • Mortality at 60 days: 17% in low-dose arm vs. 30% in intermediate-dose arm vs. 41% in high-dose arm ($P = 0.06$) • AEs (leukocytosis, hyperglycemia, and secondary infections) occurred more frequently in intermediate-dose and high-dose arms than in low-dose arm; however, this result was not statistically significant.	**Key Limitation** • Small sample size **Interpretation** • The time to clinical response was significantly shorter in the low-dose DEX arm than in the intermediate- or high-dose arms. Patients in the low-dose arm had a higher probability of survival than those in the high-dose arm.

Methods	Results	Limitations and Interpretation
Open-Label Randomized Trial of High-Dose Versus Low-Dose Dexamethasone in Patients With COVID-19-Related ARDS in Argentina[10]		

Key Inclusion Criteria
• Laboratory-confirmed SAR-CoV-2 infection
• ARDS
• On MV for <72 hours
Key Exclusion Criteria
• Presumed imminent death
• Immunosuppression
• Treatment with glucocorticoids
Interventions
• High dose: DEX 16 mg IV once daily for 5 days, followed by DEX 8 mg IV once daily for 5 days (n = 49)
• Low dose: DEX 6 mg once daily IV for 10 days (n = 49)
Primary Endpoints
• Number of ventilator-free days by Day 28
• Time to discontinuation of MV
Key Secondary Endpoint
• All-cause mortality by Day 28 and Day 90
	Participant Characteristics
	• Mean age: 60 years in high-dose arm vs. 63 years in low-dose arm
	• 30% women
	Primary Outcomes
	• Median number of ventilator-free days by Day 28: 0 for both arms ($P = 0.23$)
	• No difference between arms in mean duration of MV by Day 28 (19 ± 18 days in high-dose arm vs. 25 ± 22 days in low-dose arm; $P = 0.078$). Cumulative hazard of successful discontinuation from MV was greater in high-dose arm than low-dose arm (adjusted subdistribution HR 1.84; 95% CI, 1.31–2.5; $P < 0.001$).
	Secondary Outcome
	• All-cause mortality:
	  • By Day 28: 41% in high-dose arm vs. 39% in low-dose arm ($P > 0.999$)
	  • By Day 90: 47% in both arms ($P > 0.999$)
		Key Limitations
		• Small, open-label study
		• Trial was prematurely terminated due to low enrollment rate.
		Interpretation
		• The use of a higher dose of DEX did not increase the median number of ventilator-free days in patients with ARDS due to COVID-19. However, the higher dose shortened the time to discontinuation of MV.

Key: AE = adverse event; ARDS = acute respiratory distress syndrome; BMI = body mass index; CPAP = continuous positive airway pressure; CT = computed tomography; DEX = dexamethasone; DM = diabetes mellitus; ECMO = extracorporeal membrane oxygenation; HFNC = high-flow nasal cannula; ICU = intensive care unit; IL = interleukin; IRS = intensive respiratory support; IV = intravenous; JAK = Janus kinase; LOS = length of stay; MV = mechanical ventilation; NIV = noninvasive ventilation; OS = ordinal scale; the Panel = the COVID-19 Treatment Guidelines Panel; PaO_2/FiO_2 = ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; PCR = polymerase chain reaction; PEEP = positive end-expiratory pressure; PO = orally; RCT = randomized controlled trial; RDV = remdesivir; SAE = serious adverse event; SOC = standard of care; SOFA = sequential organ failure assessment; TB = tuberculosis

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Table 5b. Inhaled Corticosteroids: Selected Clinical Data

Last Updated: December 16, 2021

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

Methods	Results	Limitations and Interpretation
PRINCIPLE: Open-Label RCT of Inhaled Budesonide in Nonhospitalized Patients With COVID-19[1]		
Key Inclusion Criteria • Aged ≥65 years or aged ≥50 years with comorbidities • PCR-confirmed or suspected COVID-19 • ≤14 days of symptoms **Key Exclusion Criteria** • Already taking inhaled or systemic corticosteroids • Unable to use an inhaler • Contraindication to inhaled budesonide **Interventions** • Usual care plus budesonide 800 mcg inhaled twice daily for 14 days (n = 1,069) • Usual care (n = 787) **Primary Endpoints** • COVID-19-related hospitalization or death up to 28 days from randomization • Time to reported recovery up to 28 days from randomization	**Participant Characteristics** • Mean age 64.2 years; 52% women; 92% White • 81% with comorbidities • Median time from symptom onset to randomization: 6 days **Primary Outcomes** • Percentage of patients who were hospitalized or died due to COVID-19 within 28 days: 6.8% in budesonide arm vs. 8.8% in usual care arm (OR 0.75; 95% CrI, 0.55–1.03). • Median time to reported recovery: 11.8 days in budesonide arm vs. 14.7 days in usual care arm (HR 1.21; 95% CrI, 1.08–1.36).	**Key Limitations** • Open-label trial • Primary endpoint of time to reported recovery based on participant self-report **Interpretation** • Inhaled budesonide reduced time to reported recovery but not COVID-19-related hospitalization or death. • The clinical significance of self-reported time to recovery in an open-label study is unclear.
STOIC: Open-Label, Phase 2 RCT of Inhaled Budesonide in Nonhospitalized Adults With Early COVID-19[2]		
Key Inclusion Criteria • Aged ≥18 years • ≤7 days of symptoms **Key Exclusion Criteria** • Use of inhaled or systemic glucocorticoids in past 7 days • Known allergy or contraindication to budesonide	**Participant Characteristics** • Mean age 45 years; 58% women • 9% with CVD, 5% with DM • 95% with positive SARS-CoV-2 RT-PCR result • Median time from symptom onset to randomization: 3 days	**Key Limitations** • Small, open-label trial • Early termination after statistical analysis determined that additional participants would not alter study outcome

Methods	Results	Limitations and Interpretation
STOIC: Open-Label, Phase 2 RCT of Inhaled Budesonide in Nonhospitalized Adults with Early COVID-19[2], continued		
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	**Primary Outcomes** • Median duration of budesonide use: 7 days. • Percentage of patients with COVID-19-related urgent care visit or hospitalization: 1% in budesonide arm vs.14% in usual care arm (relative risk reduction 91%).	**Interpretation** • In adult outpatients with mild COVID-19, inhaled budesonide may reduce the need for urgent care or ED assessment and/or hospitalization.
Phase 3, Double-Blind RCT of Inhaled Ciclesonide in Nonhospitalized Patients With COVID-19[3]		

Key Inclusion Criteria
• Aged ≥12 years
• Positive SARS-CoV-2 molecular or antigen diagnostic test result in previous 72 hours
• ≥1 symptom of fever, cough, or dyspnea
Key Exclusion Criteria
• Taken inhaled or intranasal corticosteroid within 14 days of enrollment or systemic corticosteroid within 90 days of enrollment
• Unable to use an inhaler
Interventions
• Ciclesonide MDI 160 µg/actuation, 2 actuations twice a day for 30 days (n = 197)
• Placebo MDI twice a day for 30 days (n = 203)
Primary Endpoint
• Time to alleviation of all COVID-19-related symptoms by Day 30
Key Secondary Endpoints
• Alleviation of COVID-19-related symptoms by Day 30
• ED visit or hospital admission for COVID-19 by Day 30
• Hospital admission or death by Day 30
	Participant Characteristics
	• Mean age 43.3 years; 55.3% women; 86.3% White
	• Mean BMI 29.4
	• 22.3% with HTN, 7.5% with type 2 DM
	• Higher rates of DM and asthma in ciclesonide arm
	Primary Outcome
	• Median time to alleviation of all COVID-19-related symptoms: 19.0 days in ciclesonide arm vs. 19.0 days in placebo arm (HR 1.08; 95% CI, 0.84–1.38).
	Secondary Outcomes
	• By Day 30, percentage of patients in whom the following outcomes occurred:
	  • Alleviation of COVID-19-related symptoms: 70.6% in ciclesonide arm vs. 63.5% in placebo arm.
	  • Subsequent ED visit or hospital admission for COVID-19: 1.0% in ciclesonide arm vs. 5.4% in placebo arm (OR 0.18; 95% CI, 0.04–0.85).
	  • Hospital admission or death: 1.5% in ciclesonide arm vs. 3.4% in placebo arm (OR 0.45; 95% CI, 0.11–1.84).
	• No deaths by Day 30 in either arm.
		Key Limitations
		• ED or hospitalization outcome based on small number of events
		• Primary endpoint of time to alleviation of all symptoms based on participant self-report
		Interpretation
		• Inhaled ciclesonide did not reduce time to reported recovery.
		• The robustness of the conclusion that inhaled ciclesonide reduced COVID-19-related ED visits or hospitalization is uncertain; there were only a small number of events, which is most likely due to the relatively low rate of comorbidities in the study population.

Methods	Results	Limitations and Interpretation
CONTAIN: Double-Blind RCT of Inhaled and Intranasal Ciclesonide in Nonhospitalized Patients With COVID-19[4]		
Key Inclusion Criteria • Aged ≥18 years • Positive SARS-CoV-2 molecular diagnostic test result • ≥1 symptom of fever, cough, or shortness of breath • Symptom duration ≤6 days **Key Exclusion Criteria** • Already taking an inhaled corticosteroid or taken PO or IM corticosteroids within 7 days of enrollment • Unable to use an inhaler • No respiratory symptoms • Use of oxygen at home • COVID-19 vaccinated **Interventions** • Ciclesonide MDI 600 µg/actuation and intranasal ciclesonide 100 µg, both twice a day for 14 days (n = 105) • Saline placebo MDI and intranasal saline, both twice a day for 14 days (n = 98) **Primary Endpoint** • Resolution of fever and all respiratory symptoms at Day 7 **Key Secondary Endpoints** • Resolution of fever and all respiratory symptoms at Day 14 • Hospital admission by Day 14	**Participant Characteristics** • Median age 35 years; 54% women; 61% White • 20% with comorbid condition **Primary Outcome** • Percentage of patients with resolution of fever and all respiratory symptoms at Day 7: 40% in ciclesonide arm vs. 35% in placebo arm (adjusted risk difference 5.5%; 95% CI, -7.8% to 18.8%). **Secondary Outcomes** • Percentage of patients with resolution of fever and all respiratory symptoms at Day 14: 66% in ciclesonide arm vs. 58% in placebo arm (adjusted risk difference 7.5%; 95% CI, -5.9% to 20.8%). • Percentage of patients who were admitted to the hospital by Day 14: 6% in ciclesonide arm vs. 3% in placebo arm (adjusted risk difference 2.3%; 95% CI, -3.0% to 7.6%).	**Key Limitation** • Small study with a relatively young, healthy population **Interpretation** • The use of inhaled ciclesonide plus intranasal ciclesonide did not improve resolution of fever and respiratory symptoms in nonhospitalized patients with COVID-19.

Key: BMI = body mass index; CVD = cardiovascular disease; DM = diabetes mellitus; ED = emergency department; HTN = hypertension; IM = intramuscular; MDI = metered dose inhaler; the Panel = the COVID-19 Treatment Guidelines Panel; PCR = polymerase chain reaction; PO = oral; RCT = randomized controlled trial; RT-PCR = reverse transcription polymerase chain reaction

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Interleukin-6 Inhibitors

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Interleukin (IL)-6 is a pleiotropic, proinflammatory cytokine produced by a variety of cell types, including lymphocytes, monocytes, and fibroblasts. Infection by SARS-CoV induces a dose-dependent production of IL-6 from bronchial epithelial cells.[1] COVID-19-associated systemic inflammation and hypoxemic respiratory failure can be associated with heightened cytokine release, as indicated by elevated blood levels of IL-6, C-reactive protein (CRP), D-dimer, and ferritin.[2-4] It is hypothesized that modulating IL-6 levels or the effects of IL-6 may reduce the duration and/or severity of COVID-19.

There are 2 classes of Food and Drug Administration (FDA)-approved IL-6 inhibitors: anti-IL-6 receptor monoclonal antibodies (mAbs) (e.g., tocilizumab, sarilumab) 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 tocilizumab and sarilumab in hospitalized patients who require supplemental oxygen, high-flow oxygen, noninvasive ventilation (NIV), or mechanical ventilation.
- The Panel **recommends against** the use of anti-IL-6 mAb therapy (i.e., **siltuximab**) for the treatment of COVID-19, except in a clinical trial **(BIII)**.

Additional Considerations

- Tocilizumab and sarilumab **should be used with caution** in patients with COVID-19 who belong to populations that have not been adequately represented in clinical trials. This includes patients who are significantly immunosuppressed, particularly those who have recently received other biologic immunomodulating drugs, and patients with any of the following:
  - Alanine transaminase levels >5 times the upper limit of normal
  - A high risk for gastrointestinal perforation
  - An uncontrolled serious bacterial, fungal, or non-SARS-CoV-2 viral infection
  - Absolute neutrophil counts <500 cells/μL
  - Platelet counts <50,000 cells/μL
  - Known hypersensitivity to tocilizumab or sarilumab
- Tocilizumab and sarilumab should only be given in combination with a course of dexamethasone or an alternative corticosteroid at a dose that is equivalent to dexamethasone 6 mg. See Corticosteroids for more information.
- Some clinicians would assess the patient's clinical response to dexamethasone before deciding whether tocilizumab or sarilumab is needed.
- In both the REMAP-CAP and the RECOVERY trials, 29% of patients received a second dose of tocilizumab at the discretion of their treating physician. However, there is insufficient evidence for the Panel to recommend either for or against a second dose of tocilizumab.[5,6]
- Cases of severe and disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with tocilizumab and corticosteroids.[7,8] Many clinicians would initiate empiric

treatment (e.g., with the antiparasitic drug ivermectin) with or without serologic testing in patients who are from areas where *Strongyloides* is endemic (i.e., tropical, subtropical, or warm temperate areas).[9]

Rationale

The results of the RECOVERY and REMAP-CAP trials provide consistent evidence that tocilizumab, when coadministered with corticosteroids, offers a modest survival benefit in certain patients with COVID-19 who are severely ill, who are rapidly deteriorating and have increasing oxygen needs, and who have a significant inflammatory response.[5,6] However, the Panel found it challenging to define the specific patient populations that would benefit from this intervention. If tocilizumab is not available, sarilumab may be used as an alternative because it has demonstrated a similar clinical benefit in improving survival and reducing the duration of organ support in the REMAP-CAP trial.[10] However, the Panel recommends **sarilumab** only when tocilizumab is not available or is not feasible to use **(BIIa)** because the evidence of efficacy is more extensive for tocilizumab than for sarilumab. In addition, sarilumab is currently only approved for use as a subcutaneous (SQ) injection in the United States.

The data on the efficacy of siltuximab in patients with COVID-19 are currently limited.[11]

Anti-Interleukin-6 Receptor Monoclonal Antibodies

Tocilizumab

Tocilizumab is a recombinant humanized anti-IL-6 receptor mAb that is approved by the FDA for use in patients with rheumatologic disorders and cytokine release syndrome induced by chimeric antigen receptor T cell therapy. Tocilizumab can be administered as an intravenous (IV) infusion or an SQ injection. The IV formulation should be used to treat cytokine release syndrome.[12]

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 5c.

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).[13-17]

Subsequently, patients in the 2 largest randomized controlled trials that evaluated the use of tocilizumab, REMAP-CAP and RECOVERY, received corticosteroids as part of standard of care. Both studies reported a survival benefit of tocilizumab in certain patients, including patients who exhibited rapid respiratory decompensation associated with an inflammatory response. REMAP-CAP enrolled critically ill patients who were within 24 hours of receiving respiratory support in an intensive care unit. The patients were randomized to receive open-label tocilizumab or usual care. In-hospital mortality was 28% in the tocilizumab arm and 36% in the usual care arm.[5] The RECOVERY trial enrolled hospitalized patients with COVID-19 into an open-label platform trial that included several treatment options.[6] A subset of all trial participants who had hypoxemia and CRP levels ≥75 mg/L were offered enrollment into a second randomization that compared the use of tocilizumab to usual care. In this subgroup, the 28-day mortality was 31% in the tocilizumab arm and 35% in the usual care arm. For additional findings from the REMAP-CAP and RECOVERY trials and the rationale for using tocilizumab in certain hospitalized patients who are exhibiting rapid respiratory decompensations due to COVID-19, see Therapeutic Management of Hospitalized Adults With COVID-19.

In contrast to the REMAP-CAP and RECOVERY trials, the REMDACTA trial did not find a survival benefit of tocilizumab. The trial randomized hospitalized patients with COVID-19, most of whom required NIV or high-flow oxygen support, to receive tocilizumab or placebo. All the patients received remdesivir and most received corticosteroids. Tocilizumab use did not reduce 28-day mortality among these patients (18% of patients died in the tocilizumab arm vs. 20% in the placebo arm).[18]

Clinical Trials

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

Adverse Effects

The primary laboratory abnormalities reported with tocilizumab treatment are elevated liver enzyme levels that appear to be dose dependent. Neutropenia or thrombocytopenia are uncommon. In randomized trials, no excess secondary infections were seen among patients who received combination therapy compared to control patients. Additional adverse effects of tocilizumab, such as serious infections (e.g., tuberculosis [TB], bacterial or fungal infections) and bowel perforation, have been reported.[19]

Considerations in Pregnancy

There are insufficient data to determine whether there is a tocilizumab-associated risk for major birth defects or miscarriage. As pregnancy progresses, mAbs are actively transported across the placenta (with the greatest transfer occurring during the third trimester), and this may affect immune responses in the exposed fetus. Given the paucity of data, current recommendations advise against the use of tocilizumab during pregnancy.[20] Whether to use tocilizumab during pregnancy should be a joint decision between the pregnant individual and their health care provider, and the decision-making process should include a discussion of the potential risks and benefits.

Considerations in Children

See Therapeutic Management of Hospitalized Children With COVID-19 for the Panel's recommendations regarding the use of tocilizumab in children.

Drug Availability

On June 24, 2021, the FDA issued an Emergency Use Authorization (EUA) for the use of tocilizumab in combination with corticosteroids in hospitalized adults and children aged ≥2 years with COVID-19 who require supplemental oxygen, NIV, mechanical ventilation, or extracorporeal membrane oxygenation.[21] Per this EUA, if a patient's clinical signs or symptoms worsen or do not improve after the first dose of tocilizumab, 1 additional IV infusion of tocilizumab may be administered at least 8 hours after the initial 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 5c.

An adaptive Phase 2 and 3 double-blind 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). This trial did not show a clinical benefit of sarilumab in hospitalized patients who were receiving supplemental oxygen.[22]

A similar adaptive design study conducted in the United States in patients with severe and critical COVID-19 also failed to show a benefit of sarilumab. In this placebo-controlled trial, there was a reduction in mortality by Day 22 among the sarilumab recipients with critical COVID-19 pneumonia who required mechanical ventilation and received corticosteroids at baseline. However, due to the small sample size, this result was not statistically significant.[23]

In the REMAP-CAP trial, the efficacy results for sarilumab were similar to those for tocilizumab. Compared to the patients in the standard of care arm (n = 418), those in the sarilumab arm (n = 485) had more organ support-free days (OR 1.50; 95% CrI, 1.13–2.00) and a greater likelihood of survival while hospitalized (OR 1.51; 95% CrI, 1.06–2.20). A notable limitation to the sarilumab findings in the REMAP-CAP trial is that patients in the standard of care arm were enrolled earlier in the pandemic than those in the sarilumab arm. Randomization closed on November 2020 for the standard of care arm and continued through April 2021 for the sarilumab arm.[10]

Clinical Trials

See ClinicalTrials.gov for a list of clinical trials 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. As pregnancy progress, mAbs are actively transported across the placenta (with the greatest transfer occurring during the third trimester), and this may affect immune responses in the exposed fetus.

Considerations in Children

See Therapeutic Management of Hospitalized Children With COVID-19 for the Panel's recommendations regarding the use of sarilumab in children.

Drug Availability

The IV formulation of sarilumab is not approved by the FDA. 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 1 hour.[24]

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 administered as an IV infusion.

Clinical Data for COVID-19

There are limited data on the efficacy of siltuximab in patients with COVID-19.[11] There is no information on clinical experiences with 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 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. As pregnancy progresses, mAbs are transported across the placenta (with the greatest transfer occurring during the third trimester), and this may affect immune responses in the exposed fetus.

Considerations in Children

The safety and efficacy of siltuximab have not been established in pediatric patients.

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Table 5c. Interleukin-6 Inhibitors: Selected Clinical Data

Last Updated May 31, 2022

The clinical trials described in this table do not represent all the trials that the Panel reviewed while developing the recommendations for IL-6 inhibitors. The studies summarized below are those that have had the greatest impact on the Panel's recommendations.

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

Methods	Results	Limitations and Interpretation
RECOVERY: Open-Label RCT of Tocilizumab and Usual Care in Hospitalized Adults With COVID-19 in the United Kingdom[1]		

Key Inclusion Criteria
• Evidence of COVID-19 progression ≤21 days after initial randomization to an intervention within the RECOVERY protocol, defined as:
  • SpO_2 <92% on room air or receipt of supplemental oxygen; *and*
  • CRP ≥75 mg/L
Key Exclusion Criterion
• Non-SARS-CoV-2 infection
Interventions
• Single weight-based dose of tocilizumab (maximum 800 mg) and possible second dose (n = 2,022)
• Usual care (n = 2,094)
Primary Endpoint
• 28-day all-cause mortality
Key Secondary Endpoints
• Time to discharge from hospital, alive, within 28 days
• Among those not on MV at enrollment, death or receipt of MV within 28 days
	Participant Characteristics
	• Mean age 64 years; 67% men; 76% White
	• 95% with PCR-confirmed SARS-CoV-2 infection
	• At baseline:
	  • 45% on conventional oxygen
	  • 41% on HFNC oxygen or NIV
	  • 14% on MV
	  • 82% on corticosteroids
	Primary Outcomes
	• 28-day all-cause mortality: 31% in tocilizumab arm vs. 35% in usual care arm (rate ratio 0.85; 95% CI, 0.76–0.94; $P = 0.003$)
	• 28-day all-cause mortality among those who required MV at baseline: 49% in tocilizumab arm vs. 51% in usual care arm (risk ratio 0.93; 95% CI, 0.74–1.18)
	Secondary Outcomes
	• Proportion discharged alive from hospital within 28 days: 57% in tocilizumab arm vs. 50% in usual care arm (rate ratio 1.22; 95% CI, 1.12–1.33; $P < 0.0001$)
	• Median time to discharge: 19 days in tocilizumab arm vs. 28 days in usual care arm
	• Proportion not on MV at baseline who died or required MV within 28 days: 35% in tocilizumab arm vs. 42% in usual care arm (rate ratio 0.84; 95% CI, 0.77–0.92; $P < 0.0001$)
		Key Limitations
		• Arbitrary CRP ≥75 mg/L cutoff for enrollment
		• Difficult to define exact subset of patients in RECOVERY cohort who were subsequently selected for secondary randomization/tocilizumab trial
		Interpretation
		• Among hospitalized COVID-19 patients with hypoxemia and elevated CRP, tocilizumab was associated with reduced all-cause mortality and shorter time to discharge alive.

Methods	Results	Limitations and Interpretation
REMAP-CAP: Open-Label, Adaptive-Platform RCT of Tocilizumab and Sarilumab in Adults With COVID-19 in 21 Countries in Europe and North America[2,3]		

Key Inclusion Criteria
• ICU admission
• Suspected or laboratory-confirmed COVID-19
• Receipt of MV, NIV, or cardiovascular support
Key Exclusion Criteria
• >24 hours after ICU admission
• Presumption of imminent death
• Immunosuppression
• ALT >5 times ULN
Interventions
• SOC plus 1 of the following (drug selection based on provider preference, availability, or adaptive probability):
  • Single dose tocilizumab 8 mg/kg IV and possible second dose in 12–24 hours (n = 952)
  • Single dose sarilumab 400 mg IV (n = 485)
• SOC alone (n = 406)
Primary Endpoint
• Composite of in-hospital mortality and organ support-free days to Day 21 (ordinal scale)
Key Secondary Endpoint
• In-hospital survival
	Participant Characteristics
	• Mean age 60 years; 69% men; 75% White
	• 86% PCR-confirmed SARS-CoV-2 infection
	• Median 14 hours from ICU admission to enrollment
	• At baseline:
	  • 68% on HFNC oxygen or NIV
	  • 32% on MV
	  • On corticosteroids: 67% in SOC arm, 82% in tocilizumab arm, 89% in sarilumab arm
	Primary Outcomes
	Tocilizumab vs. SOC
	• Median organ support-free days: 7 in tocilizumab arm vs. 0 in SOC arm
	• Improved composite outcome, by ordinal scale: median aOR 1.46 (95% CrI, 1.13–1.87)
	  • Highest CRP tercile: aOR 1.87 (95% CrI, 1.35–2.59)
	• Outcomes consistent across subgroups according to oxygen requirement at baseline
	Sarilumab vs. SOC
	• Median organ support-free days: 9 in sarilumab arm vs. 0 in SOC arm
	• Improved composite outcome, by ordinal scale: median aOR 1.50 (95% CrI, 1.13–2.00)
	  • Highest CRP tercile: aOR 1.85 (95% CrI, 1.24–2.69)
	• Outcomes consistent across subgroups according to oxygen requirements at study entry
	Secondary Outcomes
	Tocilizumab vs. SOC
	• In-hospital survival: 66% in tocilizumab arm vs. 63% in SOC arm (aOR 1.42; 95% CrI, 1.05–1.93)
	Sarilumab vs. SOC
	• In-hospital survival: 67% in sarilumab arm vs. 63% in SOC arm (aOR 1.51; 95% CrI, 1.06–2.20)
		Key Limitation
		• The SOC arm closed in November 2020, after which patients were randomized to active arms only; enrollment in the tocilizumab and sarilumab arms was partially nonconcurrent with the SOC arm, and although comparisons to the SOC arm were adjusted for time period, there is a possibility of bias.
		Interpretation
		• Among patients with respiratory failure who were within 24 hours of ICU admission, the tocilizumab and sarilumab arms had higher rates of in-hospital survival and shorter durations of organ support than the SOC arm.
		• These results were reported in a preprint and are consistent with those for a smaller cohort previously published in a peer-reviewed article.
		• The treatment effect appeared to be strongest in the highest CRP tercile.
		• Tocilizumab and sarilumab were similarly effective, with a 99% probability of noninferiority of sarilumab.

Methods	Results	Limitations and Interpretation
COVACTA: Double-Blind RCT of Tocilizumab in Hospitalized Adults With COVID-19 in 9 Countries in Europe and North America[4]		
Key Inclusion Criteria • PCR-confirmed SARS-CoV-2 infection • Hypoxemia • Bilateral chest infiltrates **Key Exclusion Criteria** • Presumption of imminent death • Presence of active non-SARS-CoV-2 infection **Interventions** • Single dose of tocilizumab 8 mg/kg and possible second dose, plus SOC (n = 294) • Placebo plus SOC (n = 144) **Primary Endpoint** • Day 28 clinical status (ordinal score) **Key Secondary Endpoints** • Time to discharge • ICU LOS • Day 28 mortality	**Participant Characteristics** • Mean age 61 years; 70% men; 58% White • 30% on HFNC oxygen or NIV • 38% on MV • 25% with multiorgan failure • Received corticosteroids at entry or during follow-up: 36% in tocilizumab arm, 55% in placebo arm **Primary Outcome** • Day 28 clinical status: no significant difference between arms (P = 0.31) **Secondary Outcomes** • Median time to discharge: 20 days in tocilizumab arm vs. 28 days in placebo arm (HR 1.35; 95% CI, 1.02–1.79) • Median ICU LOS: 9.8 days in tocilizumab arm vs. 15.5 days in placebo arm (difference 5.8 days, 95% CI, –15.0 to 2.9) • Day 28 mortality: 20% in tocilizumab arm vs. 19% in placebo arm (P = 0.94)	**Key Limitations** • Modest power to detect differences in Day 28 clinical status • More patients in placebo arm than tocilizumab arm received corticosteroids. **Interpretation** • There was no difference in Day 28 clinical status or survival between the tocilizumab and placebo recipients. • The median time to discharge was significantly shorter in the tocilizumab arm than in the placebo arm. • Although the result was not statistically significant, the tocilizumab arm had a shorter ICU LOS than the placebo arm.

Methods	Results	Limitations and Interpretation
EMPACTA: Double-Blind RCT of Tocilizumab in Hospitalized Adults With COVID-19 in 6 Countries in North America, South America, and Africa[5]		

Key Inclusion Criteria
• PCR-confirmed SARS-CoV-2 infection
• COVID-19 pneumonia
Key Exclusion Criteria
• Presumption of imminent death
• Receiving NIV or MV
Interventions
• Single dose of tocilizumab 8 mg/kg plus SOC, possible second dose (n = 249)
• Placebo plus SOC (n = 128)
Primary Endpoint
• Progression to MV, ECMO, or death by Day 28
Key Secondary Endpoints
• Time to hospital discharge or readiness for discharge (ordinal score)
• All-cause mortality by Day 28
	Participant Characteristics
	• Mean age 56 years; 59% men; 56% Hispanic/Latinx, 15% Black/African American, 13% American Indian/Alaska Native
	• 84% with elevated CRP
	• Concomitant medications:
	  • Corticosteroids: 80% in tocilizumab arm, 88% in placebo arm
	  • RDV: 53% in tocilizumab arm, 59% in placebo arm
	Primary Outcome
	• Proportion who progressed to MV, ECMO, or death by Day 28: 12% in tocilizumab arm vs. 19% in placebo arm (HR 0.56; 95% CI, 0.33–0.97; $P = 0.04$)
	Secondary Outcomes
	• Median time to hospital discharge or readiness for discharge: 6.0 days in tocilizumab arm vs. 7.5 days in placebo arm (HR 1.16; 95% CI, 0.91–1.48)
	• All-cause mortality by Day 28: 10.4% in tocilizumab arm vs. 8.6% in placebo arm (95% CI, –5.2 to 7.8)
		Key Limitation
		• Moderate sample size
		Interpretation
		• In patients with COVID-19 pneumonia, tocilizumab reduced the likelihood of progression to MV, ECMO, or death by Day 28 but did not reduce 28-day all-cause mortality.

Methods	Results	Limitations and Interpretation
BACC Bay: Double-Blind RCT of Tocilizumab in Hospitalized Adults With COVID-19 in the United States[6]		

Key Inclusion Criteria
• Laboratory-confirmed SARS-CoV-2 infection
• ≥2 of the following conditions:
  • Fever >38°C
  • Pulmonary infiltrates
  • Need for supplemental oxygen
• ≥1 of the following laboratory criteria:
  • CRP ≥50 mg/L
  • D-dimer >1,000 ng/mL
  • LDH ≥250 U/L
  • Ferritin >500 ng/mL
Key Exclusion Criteria
• Receipt of supplemental oxygen at rate >10 L/min
• Recent use of biologic agents or small-molecule immunosuppressive therapy
• Receipt of immunosuppressive therapy that increased risk for infection
Interventions
• Tocilizumab 8 mg/kg plus usual care (n = 161)
• Placebo plus usual care (n = 81)
Primary Endpoint
• Receipt of MV or death, according to a time to event analysis; data censored at Day 28
Key Secondary Endpoints
• Clinical worsening by Day 28 (ordinal score)
• Discontinuation of supplemental oxygen among patients receiving it at baseline
	Participant Characteristics
	• Median age 60 years; 58% men; 45% Hispanic/Latinx, 43% White
	• 50% with BMI ≥30; 49% with HTN; 31% with DM
	• 80% receiving oxygen ≤6 L/min; 4% receiving HFNC oxygen; 16% receiving no supplemental oxygen
	• Concomitant medications:
	  • Corticosteroids: 11% in tocilizumab arm, 6% in placebo arm
	  • RDV: 33% in tocilizumab arm, 29% in placebo arm
	Primary Outcome
	• Day 28 MV or death: 11% in tocilizumab arm vs. 12% in placebo arm (HR 0.83; 95% CI, 0.38–1.81; $P = 0.64$)
	Secondary Outcomes
	• Proportion with clinical worsening of disease by Day 28: 19% in tocilizumab arm vs. 17% in placebo arm (HR 1.11; 95% CI, 0.59–2.10; $P = 0.73$)
	• Median days to discontinuation of oxygen: 5.0 in tocilizumab arm vs. 4.9 in placebo arm ($P = 0.69$)
		Key Limitations
		• Wide confidence intervals due to small sample size and low event rates
		• Few patients received RDV or corticosteroids
		Interpretation
		• There was no benefit of tocilizumab in preventing MV or death, reducing the risk of clinical worsening, or reducing the time to discontinuation of oxygen. This could be due to the low rate of concomitant corticosteroid use among the study participants.

Methods	Results	Limitations and Interpretation
Double-Blind, RCT of Sarilumab in Hospitalized Adults With Severe or Critical COVID-19 in 11 Countries in Europe, North America, South America, and Asia[7]		

Key Inclusion Criteria
• COVID-19 pneumonia
• Requirement for supplemental oxygen or intensive care
Key Exclusion Criteria
• Low probability of surviving or remaining at study site
• Dysfunction of ≥2 organ systems and need for ECMO or renal replacement therapy
Interventions
• Sarilumab 400 mg IV (n = 173)
• Sarilumab 200 mg IV (n = 159)
• Placebo (n = 84)
Primary Endpoint
• Time to clinical improvement of ≥2 points on a 7-point scale
Key Secondary Endpoint
• Survival at Day 29
	Participant Characteristics
	• Median age 59 years; 63% men; 77% White, 36% Hispanic/Latinx
	• 39% on HFNC oxygen, MV, or NIV
	• 42% with BMI ≥30; 43% with HTN; 26% with type 2 DM
	• 20% received systemic corticosteroids before receiving intervention; 63% received ≥1 dose of corticosteroids during the study
	Primary Outcomes
	• Median time to clinical improvement: 10 days in each sarilumab arm, 12 days in placebo arm
	  • Sarilumab 200 mg arm vs. placebo arm: HR 1.03; 95% CI, 0.75–1.40; $P = 0.96$
	  • Sarilumab 400 mg arm vs. placebo arm: HR 1.14; 95% CI, 0.84–1.54; $P = 0.34$
	Secondary Outcome
	• Survival at Day 29: 92% in placebo arm; 90% in sarilumab 200 mg arm ($P = 0.63$ vs. placebo); 92% in sarilumab 400 mg arm ($P = 0.85$ vs. placebo)
		Key Limitation
		• Moderate sample size
		Interpretation
		• Sarilumab showed no mortality benefit or reduction in time to clinical improvement in hospitalized adults with COVID-19.

Methods	Results	Limitations and Interpretation
REMDACTA: Double-Blind RCT of Tocilizumab and Remdesivir in Hospitalized Patients With Severe COVID-19 Pneumonia in Brazil, Russia, Spain, and the United States[8]		

Key Inclusion Criteria
• Aged ≥12 years
• PCR-confirmed SARS-CoV-2 infection
• Hospitalized with pneumonia confirmed by CXR or CT and requiring supplemental oxygen >6 L/min
Key Exclusion Criteria
• eGFR <30 mL/min
• ALT or AST >5 times ULN
• Presence of non-SARS-CoV-2 infection
• Treatment with antivirals, CP, CQ, HCQ, JAK inhibitors
Interventions
• Up to 10 days RDV plus:
  • Tocilizumab 8 mg/kg IV, with second dose within 8–24 hours if indicated (n = 434)
  • Placebo (n = 215)
Primary Endpoint
• Time to discharge or ready for discharge through Day 28
Key Secondary Endpoints
• Time to MV or death through Day 28
• Day 14 clinical status (ordinal score)
• Time to death through Day 28
	Participant Characteristics
	• Mean age 59 years; 40% in tocilizumab arm and 34% in placebo arm aged ≥65 years; 63% men; 67% White
	• Respiratory support:
	  • NIV or HFNC oxygen: 78% in tocilizumab arm, 83% in placebo arm
	  • MV or ECMO: 15% in tocilizumab arm, 11% in placebo arm
	• Corticosteroid use:
	  • At baseline: 83% in tocilizumab arm, 86% in placebo arm
	  • During trial: 88% in each arm
	Primary Outcome
	• Time to discharge or ready for discharge through Day 28: 14 days in each arm (HR 0.97; 95% CI, 0.78–1.19; $P = 0.74$)
	Secondary Outcomes
	• No difference between arms:
	  • Proportion who required MV or died by Day 28: 29% in each arm; time to death not evaluable (HR 0.98; 95% CI, 0.72–1.34; $P = 0.90$)
	  • Mean ordinal score for Day 14 clinical status: 2.8 in tocilizumab arm vs. 2.9 in placebo arm ($P = 0.72$)
	  • Death by Day 28: 18% in tocilizumab arm vs. 20% in placebo arm; time to death not evaluable (HR 0.95; 95% CI, 0.65–1.39; $P = 0.79$)
		Key Limitations
		• During the trial, primary outcome changed from clinical status on Day 28 to time to discharge or ready for discharge through Day 28
		• Imbalances in patient characteristics at baseline between arms
		• Possible underrepresentation of patients with rapidly progressive disease
		Interpretation
		• Compared with placebo plus RDV, tocilizumab plus RDV did not shorten the time to discharge or ready for discharge in patients with severe COVID-19 pneumonia.
		• There was no difference in mortality between the arms.

Key: ALT = alanine transaminase; AST = aspartate transaminase; BMI = body mass index; CP = convalescent plasma; CQ = chloroquine; CRP = C-reactive protein; CT = computed tomography; CXR = chest X-ray; DM = diabetes mellitus; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; HCQ = hydroxychloroquine; HFNC = high-flow nasal cannula; HTN = hypertension; ICU = intensive care unit; IL = interleukin; IV = intravenous; JAK = Janus kinase; LDH = lactate dehydrogenase; LOS = length of stay; MV = mechanical ventilation; NIV = noninvasive ventilation; the Panel = the COVID-19 Treatment Guidelines Panel; PCR = polymerase chain reaction; RCT = randomized controlled trial; RDV = remdesivir; SOC = standard of care; SpO_2 = oxygen saturation; ULN = upper limit of normal

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

Last Updated: August 8, 2022

Janus Kinase Inhibitors

Janus kinase (JAK) inhibitors such as baricitinib and tofacitinib have been shown to improve clinical outcomes among hospitalized patients with COVID-19. The primary mechanism of JAK inhibitors is interference with phosphorylation of the signal transducer and activator of transcription (STAT) proteins[1,2] involved in vital cellular functions, including signaling, growth, and survival. These kinase inhibitors are used 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] 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]

In May 2022, the Food and Drug Administration (FDA) approved the use of baricitinib for the treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, noninvasive ventilation (NIV), mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).[5]

Recommendations

- Baricitinib or tofacitinib is recommended in combination with dexamethasone in hospitalized patients with evidence of inflammation and increasing oxygen needs. See Therapeutic Management of Hospitalized Adults With COVID-19 for the COVID-19 Treatment Guidelines Panel's (the Panel) detailed recommendations and ratings on the use of baricitinib and tofacitinib.
- 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

Several large randomized controlled trials have demonstrated that some patients who require supplemental oxygen and most patients who require a high-flow device, NIV, or mechanical ventilation benefit from the use of dexamethasone in combination with baricitinib or tofacitinib.

In the RECOVERY trial, baricitinib was associated with a survival benefit among hospitalized patients, with a treatment effect that was most pronounced among patients receiving NIV or oxygen supplementation through a high-flow device.[6] The COV-BARRIER trial also demonstrated a survival benefit from baricitinib that was most pronounced among patients receiving high-flow oxygen or NIV.[7] In the addendum to the COV-BARRIER trial, the benefit extended to patients receiving mechanical ventilation.[8] Data from the ACTT-2[9] and ACCT-4[10] trials support the overall safety of baricitinib and the potential for benefit, but neither trial studied the drug in combination with dexamethasone as standard care.

The STOP-COVID study examined the use of tofacitinib in people with COVID-19 pneumonia who were not receiving mechanical ventilation at the time of enrollment.[11] The study demonstrated a survival benefit in patients who received tofacitinib, nearly all of whom also received corticosteroids. Tofacitinib has less clinical data support than baricitinib, but tofacitinib can be used as an alternative if baricitinib is not available.

Clinical trial data on the use of JAK inhibitors, including baricitinib and tofacitinib, in patients with COVID-19 are summarized below and in Table 5d. All related treatment recommendations are reviewed in Therapeutic Management of Hospitalized Adults With COVID-19.

Monitoring, Adverse Effects, and Drug-Drug Interactions

Adverse effects of JAK inhibitors include infections (typically respiratory and urinary tract infections), reactivation of herpes virus infections, myelosuppression, transaminase elevations, and, rarely, gastrointestinal perforation. An FDA review of a large, randomized safety clinical trial in people with rheumatoid arthritis compared tofacitinib to tumor necrosis factor inhibitors over 4 years and found that tofacitinib was associated with additional serious adverse events, including heart attack or stroke, cancer, blood clots, and death.[12] Therefore, the FDA now requires 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 have not revealed significant safety signals, including thrombosis.[6,7,9-11]

A complete blood count with differential, liver enzyme, and kidney function tests should be obtained from all patients before administering baricitinib or tofacitinib and during treatment as clinically indicated. Because of the immunosuppressive effects of baricitinib, all patients receiving the drug should also be monitored for new infections.

Tofacitinib is a cytochrome P450 (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**. See Table 5f for kinase inhibitor drug characteristics and dosing information.

Baricitinib

In May 2022, the FDA approved the use of baricitinib for the treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, NIV, mechanical ventilation, or ECMO.[5] It is also FDA approved for the treatment of rheumatoid arthritis.

Baricitinib is an oral JAK inhibitor that is selective for JAK1 and JAK2. It can modulate downstream inflammatory responses via JAK1/JAK2 inhibition and has exhibited dose-dependent inhibition of IL-6-induced STAT3 phosphorylation.[13] Baricitinib has postulated antiviral effects by blocking SARS-CoV-2 from entering and infecting lung cells.[14] In macaques infected with SARS-CoV-2, baricitinib reduced inflammation and lung pathology, but an antiviral effect was not confirmed.[15]

Clinical Data for COVID-19

For additional details on clinical trial data for baricitinib, see Table 5d. For information on the Panel's recommendations for the use of baricitinib in hospitalized patients with COVID-19, see 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.

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.[16] Tofacitinib is also FDA approved for the treatment of psoriatic arthritis, juvenile idiopathic arthritis, and ulcerative colitis.[17]

Clinical Data for COVID-19

For additional details on clinical trial data for tofacitinib, see Table 5d.

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.[18] Like baricitinib, it can modulate downstream inflammatory responses via JAK1/JAK2 inhibition and has exhibited dose-dependent inhibition of IL-6-induced STAT3 phosphorylation.[13] Ruxolitinib also has postulated antiviral effects by blocking SARS-CoV-2 from entering and infecting lung cells.[14]

Clinical Data for COVID-19

A small, single-blind, Phase 2 randomized controlled trial in patients with COVID-19 in China compared ruxolitinib 5 mg orally twice daily (n = 20) with placebo (administered as vitamin C 100 mg; n = 21), both given in combination with standard of care. Treatment with ruxolitinib was associated with a nonsignificant reduction in the median time to clinical improvement (12 days for ruxolitinib recipients vs. 15 days for placebo recipients; $P = 0.15$), defined as a 2-point improvement on a 7-category ordinal scale or 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.[19] 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.

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; therefore, fetal risk cannot be ruled out.[20] Decisions regarding the administration of JAK inhibitors must include shared decision-making between pregnant individuals and their health care providers, and potential maternal benefit and fetal risks should be considered. In the decision-making process, factors to be considered 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.[21-23]

Considerations in Children

Please see Therapeutic Management of Hospitalized Children With COVID-19 for the Panel's recommendations regarding the use of baricitinib or tofacitinib in children.

Bruton's Tyrosine Kinase Inhibitors

Bruton's tyrosine kinase (BTK) is a signaling molecule of the B-cell antigen receptor and cytokine receptor pathways. The potential benefit of BTK inhibition as a treatment for COVID-19 would be a reduction in the immunopathology associated with severe disease.

Recommendation

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

Acalabrutinib

Acalabrutinib is a second-generation, oral BTK inhibitor that is FDA approved to treat B-cell malignancies (i.e., chronic lymphocytic leukemia/small lymphocytic lymphoma, mantle cell lymphoma). It has a better toxicity profile than first-generation BTK inhibitors (e.g., ibrutinib) because it has less off-target activity for other kinases.[24] Acalabrutinib is proposed for use in patients with COVID-19 because it can modulate signaling that promotes inflammation.

Clinical Data for COVID-19

Data regarding acalabrutinib are limited to the results from a prospective case series of 19 patients with severe COVID-19.[25] The small sample size and lack of a control group limit evaluation of the data to discern any clinical benefit.

Clinical Trials

Please see ClinicalTrials.gov for the latest information on studies of acalabrutinib for the treatment of COVID-19.

Ibrutinib

Ibrutinib is a first-generation BTK inhibitor that is FDA approved to treat various B-cell malignancies[26] and to prevent chronic graft-versus-host disease in stem cell transplant recipients.[27] Based on results from a small case series, ibrutinib has been theorized to reduce inflammation and protect against ensuing lung injury in patients with COVID-19.[28]

Clinical Data for COVID-19

Data regarding ibrutinib are limited to those from an uncontrolled, retrospective case series of 6 patients with COVID-19 who received the drug for a condition other than COVID-19.[28] The small sample size and lack of a control group limit evaluation of the data to discern any clinical benefit.

Clinical Trials

Please see ClinicalTrials.gov for the latest information on studies of ibrutinib for the treatment of COVID-19.

Zanubrutinib

Zanubrutinib is a second-generation, oral BTK inhibitor that is FDA approved to treat mantle cell lymphoma.[29] It has been shown to have fewer toxicities than first-generation BTK inhibitors (e.g., ibrutinib) because it has less off-target activity for other kinases.[30] 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.[26,31] Based on these data, use of BTK inhibitors that occurs during organogenesis may be associated with fetal malformations. The impact of use later in pregnancy is unknown. Risks of use should be balanced against potential benefits.

Considerations in Children

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

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Table 5d. Kinase Inhibitors: Selected Clinical Data

Last Updated: August 8, 2022

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

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

Methods	Results	Limitations and Interpretation
RECOVERY: Open-Label RCT of Baricitinib Versus Usual Care in the United Kingdom[1]		

Key Inclusion Criterion
• Hospitalized with suspected or laboratory-confirmed SARS-CoV-2 infection
Key Exclusion Criteria
• eGFR <15 mL/min/1.73m^2
• ANC <500 cells/mm^3
• Evidence of active TB
Interventions
• BAR 4 mg PO daily for 10 days or until discharge, whichever comes first (n = 4,148)
• SOC (n = 4,008)
Primary Endpoint
• 28-day mortality
Key Secondary Endpoints
• Time to discharge from hospital
• Composite of MV, ECMO, or death
	Participant Characteristics
	• Mean age 58 years; 66% men; 80% White
	• Median duration of symptoms at enrollment: 9 days
	• 91% with laboratory-confirmed SARS-CoV-2 infection
	• At baseline:
	  • 95% received corticosteroids
	  • 23% received tocilizumab
	  • 20% received remdesivir
	  • 42% received ≥1 COVID-19 vaccine
	  • 6% no supplemental oxygen required
	  • 68% simple oxygen
	  • 24% NIV
	  • 3% MV
	Primary Outcome
	• 28-day mortality: 12% in BAR arm vs. 14% in SOC arm (age-adjusted rate ratio 0.87; 95% CI, 0.77–0.98; *P* = 0.028)
	Secondary Outcomes
	• Discharge within 28 days: 80% in BAR arm vs. 78% in SOC arm (age-adjusted rate ratio 1.10; 95% CI, 1.04–1.15; *P* = 0.002)
	  • Median time to discharge: 8 days in both arms
	• Composite of MV, ECMO, or death: 16% in BAR arm vs. 17% in SOC arm (age-adjusted risk ratio 0.89; 95% CI, 0.81–0.98; *P* = 0.016)
		Key Limitation
		• Open-label study
		Interpretation
		• In patients hospitalized for COVID-19, BAR reduced the risk of death.

Methods	Results	Limitations and Interpretation
COV-BARRIER: Double-Blind, Placebo-Controlled, Randomized Trial of Baricitinib in Hospitalized Adults in 12 Countries in Asia, Europe, North America, and South America[2]		
Key Inclusion Criteria • Laboratory-confirmed SARS-CoV-2 infection • Evidence of pneumonia or active, symptomatic COVID-19 • ≥1 elevated inflammatory marker (CRP, D-dimer, LDH, or ferritin) **Key Exclusion Criteria** • MV or ECMO • Receipt of immunosuppressants (including high-dose steroids) • Prior receipt of CCP or IVIG • ANC <1,000 cells/μL • ALC <200 cells/μL • ALT or AST >5 times ULN • eGFR <30 mL/min **Interventions** • BAR 4 mg PO once daily for up to 14 days (n = 764) • Placebo (n = 761) **Primary Endpoint** • Clinical progression or death by Day 28 **Key Secondary Endpoint** • Mortality by Day 28	**Participant Characteristics** • Mean age 58 years; 63% men • 79% received corticosteroids; 19% received RDV; 13% received oxygen but no steroids **Primary Outcome** • Clinical progression or death by Day 28: 28% in BAR arm vs. 31% in placebo arm (OR 0.85; 95% CI, 0.67–1.08; $P = 0.18$) **Secondary Outcomes** • Mortality by Day 28: 8% in BAR arm vs. 13% in placebo arm (HR 0.57; 95% CI, 0.41–0.78; $P = 0.0018$) • Mortality by Day 28 for those receiving corticosteroids at baseline: 9% in BAR arm vs. 14% in placebo arm (HR 0.63; 95% CI, 0.45–0.89)	**Key Limitation** • Results from the ACTT-2 trial prompted a protocol amendment limiting enrollment to participants who required baseline oxygen. **Interpretation** • Although the primary outcome of clinical progression or death was not significantly different between arms, treatment with BAR plus SOC was associated with reduced mortality in hospitalized adults with COVID-19 who were not receiving MV (see addendum below for results for patients who required MV or ECMO). • For patients receiving oxygen but not steroids at baseline, the primary and secondary outcomes were similar to the outcomes for the overall study population.

Methods	Results	Limitations and Interpretation
COV-BARRIER Addendum: Double-Blind, Placebo-Controlled, Randomized Trial of Baricitinib in Hospitalized Adults on Mechanical Ventilation or Extracorporeal Membrane Oxygenation in Argentina, Brazil, Mexico, and the United States[3]		
Key Inclusion Criteria • Laboratory-confirmed SARS-CoV-2 infection • Evidence of pneumonia or active, symptomatic COVID-19 • ≥1 elevated inflammatory marker (CRP, D-dimer, LDH, or ferritin) • MV or ECMO at baseline **Key Exclusion Criteria** • Receipt of immunosuppressants (including high-dose steroids) • Prior receipt of CCP or IVIG • ANC <1,000 cells/μL • ALC <200 cells/μL • ALT or AST >5 times ULN • eGFR <30 mL/min **Interventions** • BAR 4 mg PO once daily for up to 14 days (n = 51) • Placebo (n = 50) **Key Endpoints** • Mortality at Day 28 • Number of ventilator-free days • Duration of hospitalization	**Participant Characteristics** • Mean age 59 years; 55% men • 86% received corticosteroids; 2% received RDV **Outcomes** • Mortality at Day 28: 39% in BAR arm vs. 58% in placebo arm (HR 0.54; 95% CI, 0.31–0.96; *P* = 0.030) • Number of ventilator-free days and duration of hospitalization: no significant difference between arms	**Key Limitations** • Very small sample size, exploratory analysis • High mortality in placebo arm **Interpretation** • In critically ill patients with COVID-19 receiving MV or ECMO, treatment with BAR and SOC (including corticosteroids) may decrease mortality.

Methods	Results	Limitations and Interpretation
ACTT-2: Double-Blind, Placebo-Controlled, Randomized Trial of Baricitinib Plus Remdesivir in Hospitalized Adults With COVID-19 in 8 Countries in Europe, North America, and Asia[4]		

Key Inclusion Criteria
• Positive SARS-CoV-2 PCR result
• Radiographic infiltrates, SpO_2 ≤94% on room air, or requiring supplemental oxygen, MV, or ECMO
Key Exclusion Criteria
• Use of glucocorticoids for COVID-19 indications
• ALT or AST >5 times ULN
• Impaired renal function
Interventions
• BAR 4 mg PO once daily for 14 days or until discharge, plus RDV for 10 days or until discharge (n = 515)
• Placebo plus RDV (n = 518)
Primary Endpoint
• Time to recovery by Day 28
Key Secondary Endpoints
• Clinical status at Day 15 as measured by OS
• Mortality at Day 28
	Participant Characteristics
	• Mean age 55 years; 63% men; 48% White, 15% Black, 10% Asian
	• At baseline:
	  • 13% no supplemental oxygen required
	  • 55% conventional oxygen
	  • 21% HFNC oxygen or NIV
	  • 11% MV or ECMO
	Primary Outcomes
	• Median time to recovery: 7 days in BAR arm vs. 8 days in placebo arm (rate ratio 1.16; 95% CI, 1.01–1.32; $P = 0.03$)
	• Median time to recovery for those receiving HFNC oxygen or NIV: 10 days in BAR arm vs. 18 days in placebo arm (rate ratio for recovery 1.51; 95% CI, 1.10–2.08)
	Secondary Outcomes
	• Improvement in clinical status at Day 15: greater in BAR arm vs. placebo arm (OR 1.3; 95% CI, 1.0–1.6)
	• Mortality at Day 28: 5% in BAR arm vs. 8% in placebo arm (HR 0.65; 95% CI, 0.39–1.09)
		Key Limitations
		• Not powered to detect difference in mortality between arms
		• Steroids not part of SOC
		Interpretation
		• Compared with RDV alone, BAR plus RDV reduced recovery time and improved clinical status, particularly for patients who received HFNC oxygen or NIV at baseline.

Methods	Results	Limitations and Interpretation
ACTT-4: Double-Blind, Placebo-Controlled, Randomized Trial of Remdesivir With Baricitinib Versus Dexamethasone for Hospitalized Patients Requiring Supplemental Oxygen in Japan, Mexico, Singapore, South Korea, and the United States[5]		

Key Inclusion Criteria
• Hospitalized and requiring conventional oxygen, HFNC oxygen, or NIV
• Laboratory-confirmed SARS-CoV-2 infection
Key Exclusion Criterion
• Receipt of CCP or >1 dose DEX 6 mg (or equivalent) or BAR before enrollment
Interventions
• RDV IV for ≤10 days plus BAR 4 mg PO daily for ≤14 days plus DEX placebo IV (n = 516)
• RDV IV for ≤10 days plus BAR placebo PO plus DEX 6 mg IV daily ≤10 days (n = 494)
Primary Endpoint
• MV-free survival by Day 29
Key Secondary Endpoints
• Clinical status at Day 15 as measured by OS
• Time to recovery
Key Safety Endpoints
• Occurrence of treatment-related AEs
• Occurrence of SAEs
	Participant Characteristics
	• Median age 58 years; 58% men; 58% White, 34% Hispanic/Latinx
	• At baseline:
	  • 85% low-flow oxygen
	  • 15% HFNC oxygen or NIV
	• Mean duration of symptoms at enrollment: 8 days
	Primary Outcome
	• MV-free survival by Day 29: 87% in BAR arm vs. 88% in DEX arm (risk difference 0.6%; 95% CI, -3.6% to 4.8%; $P = 0.91$)
	Secondary Outcomes
	• Improved clinical status at Day 15: similar between arms (OR 1.01; 95% CI, 0.80–1.27)
	  • For low-flow oxygen at baseline: OR 0.91; 95% CI, 0.70–1.17
	  • For HFNC oxygen or NIV at baseline: OR 1.64; 95% CI, 0.92–2.90
	• Median time to recovery: 6 days in BAR arm vs. 5 days in DEX arm (rate ratio 1.04; 95% CI, 0.91–1.19)
	Safety Outcomes
	• Occurrence of treatment-related AEs: 4% in BAR arm vs. 10% in DEX arm (risk difference 6.0%; 95% CI, 2.8%–9.3%; $P = 0.0004$)
	• Occurrence of SAEs: 28% in BAR arm vs. 36% in DEX arm (risk difference 7.7%; 95% CI, 1.8%–13.4%; $P = 0.012$)
	• Most SAEs and treatment-related AEs were laboratory abnormalities.
		Key Limitations
		• Study closed before completing enrollment of 1,500 as it was unlikely to show a difference between arms.
		• Not powered to analyze differences between ordinal score subgroups HFNC oxygen or NIV at baseline.
		• Few patients died or required MV, which may have decreased the power to detect a difference between arms for MV-free survival.
		• Treatment-related differences in AEs for BAR vs. DEX were mainly related to laboratory abnormalities, not clinical events. The clinical relevance of these differences in laboratory abnormalities is unclear.
		Interpretation
		• In hospitalized patients requiring conventional oxygen, HFNC oxygen, or NIV, the use of BAR or DEX resulted in similar MV-free survival by Day 29.

Methods	Results	Limitations and Interpretation
STOP-COVID: Double-Blind, Placebo-Controlled, Randomized Trial of Tofacitinib in Hospitalized Patients With COVID-19 Pneumonia in Brazil[6]		

Key Inclusion Criteria
• Laboratory-confirmed SARS-CoV-2 infection
• COVID-19 pneumonia on CXR or CT
• Hospitalized for <72 hours
Key Exclusion Criteria
• Receiving NIV, MV, or ECMO at baseline
• History of or current thrombosis
• Immunosuppression or active cancer treatment
Interventions
• Tofacitinib 10 mg PO twice daily for up to 14 days or until discharge (n = 144)
• Placebo (n = 145)
Primary Endpoint
• Mortality or respiratory failure through Day 28
Key Secondary Endpoint
• Mortality through Day 28
	Participant Characteristics
	• Mean age 56 years; 35% women
	• Median 10 days symptom onset to randomization
	• At baseline:
	  • 75% supplemental oxygen
	  • 13% HFNC oxygen
	• Use of glucocorticoids: 79% at baseline, 89% during hospitalization
	Primary Outcome
	• Mortality or respiratory failure through Day 28: 18% in tofacitinib arm vs. 29% in placebo arm (risk ratio 0.63; 95% CI, 0.41–0.97; *P* = 0.04)
	Secondary Outcome
	• Mortality through Day 28: 2.8% in tofacitinib arm vs. 5.5% in placebo arm (HR 0.49; 95% CI, 0.15–1.63)
		Key Limitations
		• Small sample size
		• RDV not available during trial
		Interpretation
		• Tofacitinib, when compared with placebo, led to a lower risk of mortality or respiratory failure among hospitalized adults with COVID-19 pneumonia, most of whom received glucocorticoids.

Key: AE = adverse event; ALC = absolute lymphocyte count; ALT = alanine transaminase; ANC = absolute neutrophil count; AST = aspartate transaminase; BAR = baricitinib; CCP = COVID-19 convalescent plasma; CRP = C-reactive protein; CT = computed tomography; CXR = chest X-ray; DEX = dexamethasone; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; HFNC = high-flow nasal cannula; IVIG = intravenous immunoglobulin; LDH = lactate dehydrogenase; MV = mechanical ventilation; NIV = noninvasive ventilation; OS = ordinal scale; the Panel = the COVID-19 Treatment Guidelines Panel; PCR = polymerase chain reaction; PO = orally; RCT = randomized controlled trial; RDV = remdesivir; SAE = serious adverse event; SOC = standard of care; SpO_2 = oxygen saturation; TB = tuberculosis; ULN = upper limit of normal

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Granulocyte-Macrophage Colony-Stimulating Factor Inhibitors

Last Updated: March 24, 2022

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a myelopoietic growth factor and pro-inflammatory cytokine that plays a central role in a broad range of immune-mediated diseases. GM-CSF, which is secreted by macrophages, T cells, mast cells, natural killer cells, endothelial cells, and fibroblasts, regulates macrophage number and function. It acts as a pro-inflammatory signal, prompting macrophages to launch an immune cascade that ultimately results in tissue damage.[1,2] GM-CSF is believed to be a key driver of lung inflammation in severe and critical COVID-19 pneumonia, operating upstream of other pro-inflammatory cytokines and chemokines.[1-6] Anti-GM-CSF monoclonal antibodies (mAbs) may mitigate inflammation by inhibiting this signaling axis upstream and thus minimizing downstream production of numerous pro-inflammatory mediators involved in the pathogenesis of COVID-19.[7] Gimsilumab, lenzilumab, namilumab, and otilimab target GM-CSF directly, neutralizing the biological function of GM-CSF by blocking the interaction of GM-CSF with its cell surface receptor.[1,8,9] Mavrilimumab targets the alpha subunit of the GM-CSF receptor, blocking intracellular signaling of GM-CSF.[8,10] None of these agents are currently FDA approved for any indication.

Recommendation

- There is insufficient evidence for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of GM-CSF inhibitors for the treatment of hospitalized patients with COVID-19.

Rationale

Clinical data are lacking to definitively establish the potential benefits and risks associated with the use of GM-CSF inhibitors in patients with COVID-19. Data from a double-blind randomized controlled trial of lenzilumab did show a significant improvement in the primary endpoint of ventilator-free survival through Day 28 among those who received the GM-CSF inhibitor.[11] However, preliminary data from a large, double-blind randomized trial of otilimab (primary endpoint: alive and free

of respiratory failure at Day 28) and published results of a small, double-blind, randomized trial of mavrilimumab (primary endpoint: proportion alive and off supplemental oxygen at Day 14) did not show a survival benefit for the GM-CSF inhibitors compared to placebo.[12-14] The study populations differed; the lenzilumab and mavrilimumab studies primarily included patients on room air or low-flow oxygen and excluded patients receiving mechanical ventilation, whereas the otilimab study included only patients receiving high-flow oxygen, noninvasive ventilation, or mechanical ventilation. Lenzilumab and mavrilimumab continue to be investigated, whereas clinical development of otilimab for the treatment of COVID-19 has ceased.

Clinical Data for COVID-19

Lenzilumab, mavrilimumab, namilumab, and otilimab have been evaluated in clinical trials in hospitalized adults with SARS-CoV-2 pneumonia.[12-15] Clinical data are not yet published for gimsilumab. The Panel's recommendations are based on the results of the available clinical studies. Selected clinical data on the use of anti-GM-CSF mAbs for the treatment of COVID-19 are summarized in Table 5e.

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.[16]

Considerations in Pregnancy

Pregnant patients have been excluded from clinical trials evaluating GM-CSF inhibitors for the treatment of COVID-19. There is insufficient evidence to recommend for or against their use in pregnant individuals with COVID-19.

Considerations in Children

There are no data on the use of GM-CSF inhibitors in children.

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Table 5e. Granulocyte-Macrophage Colony-Stimulating Factor Inhibitors: Selected Clinical Data

Last Updated: March 24, 2022

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

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

Methods	Results	Limitations and Interpretation
LIVE-AIR: Double-Blind RCT of Lenzilumab in Hospitalized Patients With Severe COVID-19 Pneumonia in the United States and Brazil[1,2]		
Key Inclusion Criteria • Hospitalized with SARS-CoV-2 pneumonia • SpO_2 ≤94% on room air or required low-flow supplemental oxygen, HFNC oxygen, or NIV **Key Exclusion Criteria** • MV or ECMO • Bacterial pneumonia, fungal or viral infection • 48-hour survival not expected • Use of IL-1 inhibitors, IL-6 inhibitors, kinase inhibitors, or mAbs within prior 8 weeks **Interventions** • 3 doses of lenzilumab 600 mg IV 8 hours apart (n = 236) • Placebo (n = 243) **Primary Endpoint** • Survival without MV through Day 28 **Key Secondary Endpoints** • Mortality • Incidence of death or requiring MV or ECMO **Exploratory Endpoint** • Survival without MV, stratified by baseline CRP	**Participant Characteristics** • Mean age 61 years; 65% men; 72% White • 55% BMI ≥30 • At baseline: 41% received HFNC oxygen or NIV • 94% received corticosteroids; 72% received RDV; 69% received corticosteroids and RDV • Median CRP 79 mg/L **Primary Outcome** • Survival without MV through Day 28: 84% in lenzilumab arm vs. 78% in placebo arm (HR 1.54; 95% CI, 1.02–2.32; $P = 0.040$) **Key Secondary Outcomes** • Mortality: 10% in lenzilumab arm vs. 14% in placebo arm (HR 0.72; 95% CI, 0.42–1.23; $P = 0.24$) • Incidence of death or requiring MV or ECMO: 15% in lenzilumab arm vs. 21% in placebo arm (HR 0.67; 95% CI, 0.41–1.10; $P = 0.11$) **Exploratory Outcome** • Survival without MV for baseline CRP <150 mg/L: 90% in lenzilumab arm vs. 79% in placebo arm (HR 2.54; 95% CI, 1.46–4.41; $P = 0.0009$)	**Key Limitations** • Not powered to detect a survival benefit • Access to supportive care differed across study sites **Interpretation** • Lenzilumab improved ventilator-free survival in participants with hypoxemia who were not receiving MV, with the greatest benefit among those with lower CRP levels.

Methods	Results	Limitations and Interpretation
MASH-COVID: Double-Blind RCT of Mavrilimumab in Hospitalized Patients With Severe COVID-19 Pneumonia and Systemic Hyperinflammation in the United States[3]		

Key Inclusion Criteria
• Hospitalization with SARS-CoV-2 pneumonia
• SpO_2 <92% on room air or required supplemental oxygen
• CRP >5 mg/dL
Key Exclusion Criteria
• MV
• ANC <1,500/mm^3
• Uncontrolled bacterial infection
Interventions
• Mavrilimumab 6 mg/kg as single IV infusion (n = 21)
• Placebo (n = 19)
Primary Endpoint
• Alive and off supplemental oxygen at Day 14
Key Secondary Endpoints
• Mortality at Day 28
• Alive without respiratory failure at Day 28
	Participant Characteristics
	• Median age 57 years; 65% men; 40% African American
	• At baseline:
	  • 50% required HFNC oxygen or NIV
	  • 65% received corticosteroids
	  • 75% received RDV
	Primary Outcome
	• Alive and off supplemental oxygen at Day 14: 57% in mavrilimumab arm vs. 47% in placebo arm (OR 1.48; 95% CI, 0.43–5.16; *P* = 0.76)
	Key Secondary Outcomes
	• Mortality at Day 28: 1 (5%) in mavrilimumab arm vs. 3 (16%) in placebo arm (HR 3.72; 95% CI, 0.39–35.79; *P* = 0.22)
	• Alive without respiratory failure at Day 28: 95% in mavrilimumab arm vs. 79% in placebo arm (OR 5.33; 95% CI, 0.54–52.7; *P* = 0.43)
		Key Limitations
		• Very small sample size
		• Ended early due to slow enrollment
		Interpretation
		• Among participants with systemic hyperinflammation and severe COVID-19 pneumonia, there was no evidence that use of mavrilimumab improved supplemental oxygen–free survival by Day 14.

Methods	Results	Limitations and Interpretation
OSCAR: Double-Blind RCT of Otilimab in Patients With Severe COVID-19 Pneumonia in 17 Countries[4]		

Key Inclusion Criteria
• Hospitalized with SARS-CoV-2 pneumonia
• Required HFNC oxygen, NIV, or MV ≤48 hours before dosing
• CRP or ferritin >ULN
Key Exclusion Criteria
• Death likely <48 hours
• Multiple organ failure
• SOFA score >10 if in ICU
• ECMO
• Dialysis
• High-dose noradrenaline (>0.15 ug/kg/min) or equivalent
• >1 vasopressor
Interventions
• Otilimab 90 mg IV as single infusion (n = 395)
• Placebo (n = 398)
Primary Endpoint
• Alive and free of respiratory failure at Day 28
Key Secondary Endpoint
• All-cause mortality at Day 60
	Participant Characteristics
	• Mean age 59 years; 72% men; 66% White
	• At baseline:
	  • 77% received HFNC oxygen or NIV; 22% received MV
	  • 83% received corticosteroids; 34% received RDV
	Primary Outcome
	• Alive and free of respiratory failure at Day 28: 71% in otilimab arm vs. 67% in placebo arm (model-adjusted difference 5.3%; 95% CI, -0.8 to 11.4; *P* = 0.09)
	Key Secondary Outcome
	• All-cause mortality at Day 60: 23% in otilimab arm vs. 24% in placebo arm (model-adjusted difference -2.4%; 95% CI, -8.0 to 3.3; *P* = 0.41)
		Key Limitations
		• Changes in SOC during study may have affected outcomes.
		Interpretation
		• For participants with severe COVID-19 pneumonia, use of otilimab did not significantly reduce the probability of respiratory failure or death.

Key: ANC = absolute neutrophil count; BMI = body mass index; CRP = C-reactive protein; ECMO = extracorporeal membrane oxygenation; GM-CSF = granulocyte-macrophage colony-stimulating factor; HFNC = high-flow nasal cannula; ICU = intensive care unit; IL = interleukin; IV = intravenous; mAb = monoclonal antibody; MV = mechanical ventilation; NIV = noninvasive ventilation; RCT = randomized controlled trial; RDV = remdesivir; SOC = standard of care; SOFA = sequential organ failure assessment; SpO_2 = oxygen saturation; ULN = upper limit of normal

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Interleukin-1 Inhibitors

Last Updated: October 19, 2021

Endogenous interleukin (IL)-1 is elevated in patients with COVID-19.[1,2] In addition, SARS-CoV-2 infection causes epithelial damage that leads to the release of IL-1 beta, which recruits inflammatory cells and induces the release of IL-1 beta in monocytes. This in turn leads to the release of more IL-1 to recruit and activate additional innate immune cells. Drugs that block the IL-1 receptor (e.g., anakinra) or drugs that block IL-1 signaling (e.g., canakinumab) can potentially interrupt this autoinflammatory loop. These drugs are being investigated as potential treatments for COVID-19.

Anakinra is a recombinant human IL-1 receptor antagonist. It is approved by the Food and Drug Administration (FDA) to treat rheumatoid arthritis and cryopyrin-associated periodic syndromes, specifically neonatal-onset multisystem inflammatory disease.[3] It is used off-label to treat severe chimeric antigen receptor T cell-mediated cytokine release syndrome and macrophage activation syndrome (MAS)/secondary hemophagocytic lymphohistiocytosis.

Canakinumab is a human monoclonal antibody that targets the beta subunit of IL-1 and is approved by the FDA for the treatment of systemic juvenile idiopathic arthritis and Still's disease.

Recommendations

- There is insufficient evidence for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of anakinra for the treatment of COVID-19.
- The Panel **recommends against** the use of **canakinumab** for the treatment of COVID-19, except in a clinical trial **(BIIa)**.

Rationale

In the SAVE-MORE trial, 594 hospitalized patients who had moderate or severe COVID-19 pneumonia and plasma-soluble urokinase plasminogen activator receptor (suPAR) levels ≥6 ng/mL were randomized to receive either anakinra or placebo. The study found that patients who received anakinra had a lower risk of clinical progression of COVID-19 than those who received placebo.[4] CORIMUNO-ANA-1, a randomized controlled trial that compared the use of anakinra to usual care in 116 hospitalized patients who were hypoxemic but did not require high-flow oxygen or ventilation, was stopped early for futility.[5] REMAP-CAP, an open-label, adaptive platform, randomized controlled trial that evaluated several immunomodulators in patients with COVID-19 who required organ support, found that anakinra was not effective in reducing the combined endpoint of in-hospital mortality and days of organ support.[6] Although the SAVE-MORE study suggests that suPAR levels could be used in risk stratification to identify populations that could benefit from IL-1 inhibition, the laboratory assay that is used to assess suPAR levels is not currently available in many countries, including the United States. After reviewing the results of the studies discussed above and taking into consideration the fact that suPAR assays are not widely available to guide the use of anakinra, the Panel has concluded that there is insufficient evidence to recommend either for or against the use of anakinra for the treatment of COVID-19 in hospitalized patients.

Finally, CAN-COVID, a randomized controlled trial that evaluated canakinumab in hospitalized patients with COVID-19 who were hypoxemic but did not require ventilatory support, reported that the use of canakinumab did not improve the likelihood of survival without invasive mechanical ventilation.[7]

Because of these results, the Panel **recommends against** the use of **canakinumab** for the treatment of COVID-19, except in a clinical trial **(BIIa)**.

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 2 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 1 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 2 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 2 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 2 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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Table 5f. Characteristics of Immunomodulators

Last Updated: December 1, 2022

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

Drug Name	Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments
Corticosteroid (Systemic) *Recommended by the Panel for the treatment of COVID-19 in certain hospitalized patients.*					

Dexamethasone (Systemic)	**Dose for COVID-19**
	• DEX 6 mg IV or PO once daily for up to 10 days or until hospital discharge, whichever comes first[1]
		• Hyperglycemia
		• Secondary infections
		• Reactivation of latent infections (e.g., HBV, HSV, strongyloidiasis, TB)
		• Cases of disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with corticosteroids and tocilizumab.
		• Psychiatric disturbances
		• Avascular necrosis
			• Blood glucose
			• BP
			• Signs and symptoms of new infection
				• Moderate CYP3A4 inducer
				• CYP3A4 substrate
					• If DEX is not available, an alternative corticosteroid (e.g., prednisone, methylprednisolone, hydrocortisone) can be used.
					• The approximate total daily dose equivalencies for these glucocorticoids to DEX 6 mg (PO or IV) are:
					  • Prednisone 40 mg
					  • Methylprednisolone 32 mg
					  • Hydrocortisone 160 mg

Drug Name	Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments
Corticosteroid (Systemic), continued					
		• Adrenal insufficiency • Increased BP • Peripheral edema • Myopathy (particularly if used with NMBAs)			
Janus Kinase Inhibitors *Baricitinib and tofacitinib: Recommended by the Panel for the treatment of COVID-19 in certain hospitalized patients.* *Ruxolitinib: Not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*					

Baricitinib[2]	**FDA-Approved Doses for COVID-19 in Adults Aged ≥18 Years**[2]
	eGFR ≥60 mL/min/1.73 m²
	• Baricitinib 4 mg PO once daily
	eGFR 30 to <60 mL/min/1.73 m²
	• Baricitinib 2 mg PO once daily
	eGFR 15 to <30 mL/min/1.73 m²
	• Baricitinib 1 mg PO once daily
	eGFR <15 mL/min/1.73 m²
	• **Not recommended**
	FDA EUA Dose for Children Aged 9–17 Years[3]
	• Same as adults
		• Lymphoma and other malignancies
		• Thrombosis
		• GI perforation
		• Treatment-related changes in lymphocytes, neutrophils, Hgb, liver enzymes
		• HSV reactivation
		• Herpes zoster
		• Secondary infections
		• Serious cardiac-related events (e.g., MI, stroke)
			• CBC with differential
			• Renal function
			• Liver enzymes
			• New infections
				• Dose modification is recommended when administering concurrently with a strong OAT3 inhibitor.	• See the FDA label[2] and EUA[3] for dosing guidance for patients with:
					  • ALC <200 cells/μL
					  • ANC <500 cells/μL
					• If increases in ALT or AST are observed and DILI is suspected, interrupt baricitinib treatment until the diagnosis of DILI is excluded.
					• Baricitinib tablets can be taken orally or crushed, dispersed in water, and given via gastrostomy tube.[2]
					Availability
					• Baricitinib is approved by the FDA for the treatment of COVID-19 for adults aged ≥18 years and is available through an FDA EUA for children aged 2–17 years who require supplemental oxygen, NIV, MV, or ECMO.[3]

Drug Name	Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments
***Janus Kinase Inhibitors**, continued*					
	FDA EUA Doses for Children Aged 2 to <9 Years[3] *eGFR ≥60 mL/min/1.73m²* • Baricitinib 2 mg PO once daily *eGFR 30 to <60 mL/min/1.73m²* • Baricitinib 1 mg PO once daily *eGFR <30 mL/min/1.73m²* • **Not recommended** **Duration of Therapy** • Up to 14 days or until hospital discharge				
Ruxolitinib	**Dose for FDA-Approved Indications** • Ruxolitinib 5–20 mg PO twice daily **Dose for COVID-19 in Clinical Trials** • Ruxolitinib 5 mg PO twice daily for 14 days[4]	• Thrombocytopenia • Anemia • Neutropenia • Liver enzyme elevations • Risk of infection • Dizziness • Headache • Diarrhea • CPK elevation • Herpes zoster	• CBC with differential • Liver enzymes • New infections	• Requires dose modification when administered with strong CYP3A4 inhibitor • Avoid use with fluconazole doses >200 mg.	• May require dose modification in patients with hepatic impairment, moderate or severe renal impairment, or thrombocytopenia
Tofacitinib	**Dose for COVID-19 in Clinical Trials** • Tofacitinib 10 mg PO twice daily for up to 14 days or until hospital discharge[5]	• Thrombotic events (e.g., PE, DVT, arterial thrombosis) • Anemia • Risk of infection • GI perforation • Diarrhea • Headache	• CBC with differential • Liver enzymes • New infections	• Requires dose modification when administered with strong CYP3A4 inhibitors or when used with a moderate CYP3A4 inhibitor that is coadministered with a strong CYP2C19 inhibitor	• Avoid use in patients with ALC <500 cells/mm³, ANC <1,000 cells/mm³, or Hgb <9 grams/dL. • May require dose modification in patients with moderate or severe renal impairment or moderate hepatic impairment

Drug Name	Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments
***Janus Kinase Inhibitors**, continued*					
		• Herpes zoster • Lipid elevations • Liver enzyme elevations • Lymphoma and other malignancies • Serious cardiac-related events (e.g., MI, stroke)		• Coadministration with strong CYP3A4 inducers **is not recommended**.	
Interleukin-6 Inhibitors					
Anti-Interleukin-6 Receptor Monoclonal Antibodies *Recommended by the Panel for the treatment of COVID-19 in certain hospitalized patients.*					
Sarilumab[6]	**Dose for COVID-19 in Clinical Trials** • Single dose of sarilumab 400 mg IV[7]	• Neutropenia • Thrombocytopenia • GI perforation • HSR • Increased liver enzymes • HBV reactivation • Infusion-related reaction	• HSR • Infusion reactions • Neutrophils • PLT • Liver enzymes	• Elevated IL-6 may downregulate CYP enzymes; thus, use of sarilumab may lead to increased metabolism of drugs that are CYP substrates. • The effects of sarilumab on CYP enzymes may persist for weeks after the drug is stopped.	• Sarilumab **is not recommended** in patients with ALT or AST >1.5 times the upper limit of the reference range, ANC <2,000 cells/mm^3, or PLT <150,000 cells/mm^3.[6] • Treatment with sarilumab may mask signs of acute inflammation or infection by suppressing fever and CRP levels. **Availability** • The IV formulation of sarilumab is not approved by the FDA, but in a clinical trial, a single SUBQ dose (using the prefilled syringe, **not** the prefilled pen) of sarilumab 400 mg was reconstituted in 100 cc 0.9% NaCl and given as an IV infusion over 1 hour.

Drug Name	Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments
Interleukin-6 Inhibitors, continued					
Anti-Interleukin-6 Receptor Monoclonal Antibodies, *continued*					
					• IV infusion of sarilumab should occur within 4 hours of its preparation; it can be stored at room temperature until administered.
Tocilizumab[8]	**FDA EUA Doses for COVID-19 in Hospitalized Patients Aged ≥2 Years** *Body Weight ≥30 kg* • Tocilizumab 8 mg/kg (maximum 800 mg) by IV infusion over 1 hour • Per the EUA, if clinical signs or symptoms worsen or do not improve following the first infusion, 1 additional dose may be administered ≥8 hours after the first dose. *Body Weight <30 kg* • Tocilizumab 12 mg/kg by IV infusion over 1 hour • Per the EUA, if clinical signs or symptoms worsen or do not improve following the first infusion, 1 additional dose may be administered ≥8 hours after the first dose.	• Infusion-related reaction • HSR • GI perforation • Hepatotoxicity • Treatment-related changes on laboratory tests for neutrophils, PLT, lipids, and liver enzymes • HBV reactivation • Secondary infections • Cases of disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with tocilizumab and corticosteroids.	• HSR • Infusion reactions • Neutrophils • PLT • Liver enzymes	• Inhibition of IL-6 may lead to increased metabolism of coadministered drugs that are CYP450 substrates. • The effects of tocilizumab on CYP enzymes may persist for weeks after the drug is stopped.	• Tocilizumab **is not recommended** in patients with ALT or AST >10 times the upper limit of the reference range, ANC <1,000 cells/mm^3, or PLT <50,000 cells/mm^3.[9] • The SUBQ formulation of tocilizumab **is not intended** for IV administration. **Availability** • IV tocilizumab, which has been approved for non-COVID-19 indications, is available commercially and through an FDA EUA for the treatment of COVID-19 in hospitalized adults and pediatric patients aged ≥2 years who are receiving systemic corticosteroids and require supplemental oxygen, NIV, MV, or ECMO. The EUA does not authorize the use of SUBQ administration of tocilizumab for the treatment of COVID-19.[9]

Drug Name	Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments
Anti-Interleukin-6 Monoclonal Antibody *Not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*					
Siltuximab	**FDA-Approved Dose for Multicentric Castleman Disease** • Siltuximab 11 mg/kg by IV infusion over 1 hour every 3 weeks[10] **Dose for COVID-19** • Dose and duration unknown	• Infusion-related reaction • HSR • GI perforation • Neutropenia • HTN • Dizziness • Rash • Pruritus • Hyperuricemia	• Neutrophils • HSR • Infusion reactions	• Elevated IL-6 may downregulate CYP enzymes; use of siltuximab may lead to increased metabolism of drugs that are CYP substrates. • The effects of siltuximab on CYP enzymes may persist for weeks after therapy is stopped.	• Siltuximab **is not recommended** in patients with ANC <1,000 cells/mm^3, Hgb >17 g/dL, or PLT <75,000 cells/mm^3.[10] • Treatment with siltuximab may mask signs of acute inflammation or infection by suppressing fever and CRP levels.
Interleukin-1 Inhibitors *Anakinra: Received an FDA EUA for the treatment of COVID-19 in certain hospitalized adults. There is insufficient evidence for the Panel to recommend either for or against its use.* *Canakinumab: Not recommended by the Panel for the treatment of COVID-19.*					
Anakinra	**FDA EUA Dose for COVID-19 in Hospitalized Patients Aged ≥18 Years** • Anakinra 100 mg SUBQ once daily for 10 days **Dose for CrCl <30 mL/min** • Anakinra 100 mg SUBQ every other day for 5 total doses over 10 days.[11]	• Neutropenia (particularly when used concomitantly with other agents that can cause neutropenia) • HSR, including anaphylaxis and angioedema • Secondary infections • Injection site reactions • Liver enzyme elevations • Hyperkalemia • Hypernatremia • Rash	• CBC with differential; assess neutrophils before starting treatment and during therapy. • BMP • Liver enzymes • Renal function	• Use with TNF-blocking agents **is not recommended** due to increased risk of infection.	• Contraindicated in patients with known hypersensitivity to proteins derived from *Escherichia coli*, anakinra, or any component of the product[11] • Patients with <1,500 neutrophils/mm^3 were excluded from participation in the SAVE-MORE study.[12]

Drug Name	Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments
Interleukin-1 Inhibitors, continued					
Canakinumab	**FDA-Approved Dose for Systemic JIA** • Canakinumab 4 mg/kg (maximum 300 mg) SUBQ every 4 weeks[13]	• HSR • Neutropenia • Nasopharyngitis • Diarrhea • Respiratory tract infections • Bronchitis • Gastroenteritis • Pharyngitis • Musculoskeletal pain • Vertigo • Abdominal pain • Injection site reactions • Liver enzyme elevations	• HSR • CBC with differential • Liver enzymes	• Binding of canakinumab to IL-1 may increase formation of CYP enzymes and alter metabolism of drugs that are CYP substrates. • Use with TNF-blocking agents **is not recommended** due to potential increased risk of infection.	• Canakinumab for IV administration is not an approved formulation in the United States.[13]
Corticosteroids (Inhaled) *Not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*					
Budesonide (Inhaled)	**Dose for COVID-19 in Clinical Trials** • Budesonide 800 mcg oral inhalation twice daily until symptom resolution or up to 14 days[14,15]	• Secondary infections • Oral thrush • Systemic AEs (less common)	• Signs of AEs involving the oral mucosa or throat, including thrush • Signs of systemic corticosteroid effects (e.g., adrenal suppression)	• CYP3A4 substrate • **Do not use** with strong CYP3A4 inhibitors.	• No comments
Ciclesonide (Inhaled)	**Dose for COVID-19 in Clinical Trials** • Ciclesonide 160 mcg as 2 MDI inhalations twice daily for 30 days[16]	• Secondary infections • Oral thrush • Systemic AEs (less common)	• Signs of AEs involving the oral mucosa or throat, including thrush • Signs of systemic corticosteroid effects (e.g., adrenal suppression)	• CYP3A4 substrate • Strong CYP3A4 inhibitors are expected to have less effect on ciclesonide exposure than on budesonide exposure.	• No comments

Key: AE = adverse event; ALC = absolute lymphocyte count; ALT = alanine transaminase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BP = blood pressure; CBC = complete blood count; CPK = creatine phosphokinase; CrCl = creatinine clearance; CRP = C-reactive protein; CYP = cytochrome P450; DEX = dexamethasone; DILI = drug-induced liver injury; DVT = deep vein thrombosis; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; GI = gastrointestinal; HBV = hepatitis B virus; Hgb = hemoglobin; HSR = hypersensitivity reaction; HSV = herpes simplex virus; HTN = hypertension; IL = interleukin; IV = intravenous; JIA = juvenile idiopathic arthritis; MDI = metered dose inhaler; MI= myocardial infarction; MV = mechanical ventilation; NaCl = sodium chloride; NIV = noninvasive ventilation; NMBA = neuromuscular blocking agents; OAT = organic anion transporter; the Panel = the COVID-19 Treatment Guidelines Panel; PE = pulmonary embolism; PLT = platelet count; PO = orally; SUBQ = subcutaneous; TB = tuberculosis; TNF = tumor necrosis factor

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Antithrombotic Therapy in Patients with COVID-19

Last Updated: December 1, 2022

Summary Recommendations

Chronic Anticoagulant and Antiplatelet Therapy

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends that patients with COVID-19 who are receiving anticoagulant or antiplatelet therapies for underlying conditions continue these medications unless significant bleeding develops or other contraindications are present **(AIII)**.
- Before prescribing ritonavir-boosted nirmatrelvir (Paxlovid) to patients who are receiving anticoagulant or antiplatelet therapy, **clinicians should carefully review the patient's concomitant medications** to evaluate potential drug-drug interactions (see Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir [Paxlovid] and Concomitant Medications). It may be necessary to modify the dosage of the antithrombotic agent, switch to another antithrombotic agent, or prescribe an alternative COVID-19 therapy.

Screening and Evaluation for Venous Thromboembolism

- There is insufficient evidence for the Panel to recommend either for or against routine screening for venous thromboembolism (VTE) in patients with COVID-19 who do not have signs or symptoms of VTE, regardless of the status of their coagulation markers.
- For hospitalized patients with COVID-19 who experience rapid deterioration of pulmonary, cardiac, or neurological function or sudden, localized loss of peripheral perfusion, the Panel recommends evaluating the patients for thromboembolic disease **(AIII)**.

Anticoagulant Treatment for Thrombosis

- The Panel recommends that when diagnostic imaging is not possible, patients with COVID-19 who are highly suspected to have thromboembolic disease be managed with therapeutic anticoagulation **(AIII)**.
- The Panel recommends that patients with COVID-19 who require extracorporeal membrane oxygenation or continuous renal replacement therapy or who have thrombosis related to catheters or extracorporeal filters be treated with antithrombotic therapy as per the standard institutional protocols for those without COVID-19 **(AIII)**.

Antithrombotic Therapy for Nonhospitalized Patients Without Evidence of Venous Thromboembolism

- In nonhospitalized patients with COVID-19, the Panel **recommends against** the use of anticoagulants and antiplatelet therapy (i.e., aspirin, P2Y12 inhibitors) for the prevention of VTE or arterial thrombosis, except in a clinical trial **(AIIa)**. This recommendation does not apply to patients with other indications for antithrombotic therapy.
- The Panel **recommends against** routinely continuing VTE prophylaxis for patients with COVID-19 after hospital discharge unless they have another indication or are participating in a clinical trial **(AIII)**. For patients discharged after COVID-19-related hospitalization who are at high risk of VTE and at low risk of bleeding, there is insufficient evidence for the Panel to recommend either for or against continuing anticoagulation unless another indication for VTE prophylaxis exists.

Antithrombotic Therapy for Hospitalized, Nonpregnant Adults Without Evidence of Venous Thromboembolism

- The Panel **recommends against** using anticoagulant or antiplatelet therapy to prevent arterial thrombosis outside of the usual standard of care for patients without COVID-19 **(AIII)**.
- In hospitalized patients, **low-molecular-weight heparin** (LMWH) or **unfractionated heparin** (UFH) is preferred over oral anticoagulants **(AIII)**. Because these types of heparin have shorter half-lives, their effects can be reversed quickly. They can also be administered intravenously or subcutaneously, and they have fewer drug-drug interactions than oral anticoagulants.
- When heparin is used, LMWH is preferred over UFH.

Summary Recommendations, continued

For adults who require low-flow oxygen and do not require intensive care unit (ICU)-level care:

- The Panel recommends the use of a **therapeutic dose of heparin** for patients with D-dimer levels above the upper limit of normal who require low-flow oxygen and who do not have an increased risk of bleeding **(CIIa)**.
  - Contraindications for the use of therapeutic anticoagulation in patients with COVID-19 are a platelet count <50 x 10^9/L, hemoglobin <8 g/dL, the need for dual antiplatelet therapy, bleeding within the past 30 days that required an emergency department visit or hospitalization, a history of a bleeding disorder, or an inherited or active acquired bleeding disorder. This list is based on the exclusion criteria from clinical trials; patients with these conditions have an increased risk of bleeding.
- In patients without VTE who have started treatment with therapeutic doses of heparin, treatment should continue for 14 days or until they are transferred to the ICU or discharged from the hospital, whichever comes first.
- The Panel recommends the use of a **prophylactic dose of heparin** for patients who do not meet the criteria for receiving therapeutic heparin or are not receiving a therapeutic dose of heparin for other reasons, unless a contraindication exists **(AIIb)**.
- The Panel **recommends against** the use of a **therapeutic dose of oral anticoagulants** for VTE prophylaxis or the prevention of COVID-19 progression, except in a clinical trial **(AIIa)**.
- There is insufficient evidence for the Panel to recommend either for or against the use of thrombolytic agents for the treatment of COVID-19.
- The Panel **recommends against** the use of antiplatelet therapy to prevent COVID-19 progression or death in noncritically ill patients **(BIIa)**.

For adults who require ICU-level care, including those receiving high-flow oxygen:

- The Panel recommends using a **prophylactic dose of heparin** as VTE prophylaxis, unless a contraindication exists **(AI)**.
- For patients who start on a therapeutic dose of heparin in a non-ICU setting due to COVID-19 and then transfer to the ICU, the Panel recommends switching from the therapeutic dose to a **prophylactic dose of heparin**, unless VTE is confirmed **(BIII)**.
- The Panel **recommends against** the use of an **intermediate dose** (e.g., enoxaparin 1 mg/kg once daily) or a **therapeutic dose of anticoagulation** for VTE prophylaxis, except in a clinical trial **(BI)**.
- There is insufficient evidence for the Panel to recommend either for or against the use of antiplatelet therapy in critically ill patients with COVID-19.

Children With COVID-19 or MIS-C

- For the Panel's recommendations on the use of antithrombotic therapy in children, see Therapeutic Management of Hospitalized Children With COVID-19 and Therapeutic Management of Hospitalized Pediatric Patients With Multisystem Inflammatory Syndrome in Children (MIS-C) (With Discussion on Multisystem Inflammatory Syndrome in Adults [MIS-A]).

Pregnant and Lactating Patients

- The Panel recommends that pregnant patients who are receiving anticoagulant or antiplatelet therapies for underlying conditions continue these medications after they receive a diagnosis of COVID-19 **(AIII)**.
- The Panel recommends the use of a **prophylactic dose of anticoagulation** for pregnant patients who are hospitalized for manifestations of COVID-19, unless a contraindication exists **(BIII)**.
- Because pregnant patients have not been included in most clinical trials evaluating therapeutic anticoagulation in the setting of COVID-19, there is insufficient evidence for the Panel to recommend either for or against the use of therapeutic anticoagulation in pregnant patients with COVID-19 who do not have evidence of VTE.
- As in nonpregnant patients, VTE prophylaxis after hospital discharge is not routinely recommended for pregnant patients **(BIII)**. Decisions to continue VTE prophylaxis in the pregnant or postpartum patient after discharge should be individualized, with consideration of concomitant VTE risk factors.
- The use of anticoagulation therapy during labor and delivery requires specialized care and planning. The management of anticoagulation therapy in pregnant patients with COVID-19 should be similar to the management used for pregnant patients with other conditions **(AIII)**.

Summary Recommendations, continued
• UFH, LMWH, and warfarin do not accumulate in breast milk and do not induce an anticoagulant effect in the newborn; therefore, they can be used by breastfeeding individuals who require VTE prophylaxis or treatment **(AIII)**.
Each recommendation in the Guidelines receives 2 ratings that reflect the strength of the recommendation and the quality of the evidence that supports it. See Guidelines Development for more information.

Association Between COVID-19 and Thromboembolism

COVID-19 has been associated with inflammation and a prothrombotic state, with increases in levels of fibrin, fibrin degradation products, fibrinogen, and D-dimer.[1,2] In some studies, elevations in these markers have been associated with worse clinical outcomes.[3,4]

Studies have reported varying incidences of venous thromboembolism (VTE) in patients with COVID-19. A meta-analysis of studies of hospitalized patients with COVID-19 who received VTE prophylaxis found an overall VTE prevalence of 14.1% (95% CI, 11.6–16.9).[5] The VTE prevalence was higher in studies that used ultrasound screening (40.3%; 95% CI, 27.0–54.3) than in studies that did not (9.5%; 95% CI, 7.5–11.7). In randomized controlled trials conducted prior to the pandemic, the incidence of VTE in hospitalized patients without COVID-19 who received VTE prophylaxis ranged from 0.3% to 1% for symptomatic VTE and from 2.8% to 5.6% for VTE overall.[6-8] In randomized trials, the VTE incidence among critically ill patients without COVID-19 who received a prophylactic dose of anticoagulants ranged from 5% to 16%, and a prospective cohort study of critically ill patients with sepsis reported a VTE incidence of 37%.[9-12]

Guidelines for the use of antithrombotic therapy in patients with COVID-19 have been released by multiple organizations, including the American College of Chest Physicians,[13] the American Society of Hematology,[14] the Anticoagulation Forum,[15] the International Society on Thrombosis and Haemostasis,[16] the Italian Society on Thrombosis and Haemostasis,[17] the National Institute for Health and Care Excellence (NICE),[18] and the Royal College of Physicians.[19]

The guidelines referenced above agree that hospitalized, nonpregnant patients with COVID-19 should receive, at a minimum, a prophylactic dose of anticoagulation to prevent VTE. The NICE guidelines state: "Consider a treatment dose of a low-molecular-weight heparin (LMWH) for young people and adults with COVID-19 who need low-flow oxygen and who do not have an increased bleeding risk." Results from clinical trials have provided further information on the safety and efficacy of different antithrombotic strategies for patients with COVID-19.

Chronic Anticoagulant or Antiplatelet Therapy

The COVID-19 Treatment Guidelines Panel (the Panel) recommends that patients with COVID-19 who are receiving anticoagulant or antiplatelet therapies for underlying medical conditions continue these medications unless significant bleeding develops or other contraindications are present **(AIII)**. Outpatients with COVID-19 who are receiving warfarin and are in isolation and unable to have international normalized ratio monitoring may be candidates for switching to direct oral anticoagulant therapy. Before prescribing ritonavir-boosted nirmatrelvir (Paxlovid) to patients who are receiving anticoagulant or antiplatelet therapy, **clinicians should carefully review the patient's concomitant medications** to evaluate potential drug-drug interactions (see Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir [Paxlovid] and Concomitant Medications). It may be necessary to modify the dosage of the antithrombotic agent, switch to another antithrombotic agent, or prescribe alternative COVID-19 therapy. Patients with a mechanical heart valve, ventricular assist device, valvular atrial fibrillation, or antiphospholipid antibody syndrome and patients who are lactating should not discontinue treatment with warfarin **(AIII)**.

Screening and Evaluation for Venous Thromboembolism

VTE guidelines for patients without COVID-19 have recommended against performing routine screening ultrasounds in critically ill patients because no study has shown that this strategy reduces the rate of subsequent symptomatic thromboembolic complications.[20] Although the incidence of thromboembolic events, especially pulmonary embolism, can be high among hospitalized patients with COVID-19, no published data demonstrate the clinical utility of using lower extremity ultrasounds as routine surveillance for deep vein thrombosis in this population.

There is insufficient evidence for the Panel to recommend either for or against routine screening for VTE in patients with COVID-19 who do not have signs or symptoms of VTE, regardless of the status of their coagulation markers. For hospitalized patients with COVID-19 who experience rapid deterioration of pulmonary, cardiac, or neurological function or sudden, localized loss of peripheral perfusion, the Panel recommends evaluating the patients for thromboembolic disease **(AIII)**.

Managing Antithrombotic Therapy in Patients With COVID-19

The Panel recommends that when diagnostic imaging is not possible, patients with COVID-19 who are highly suspected to have thromboembolic disease be managed with therapeutic anticoagulation **(AIII)**.

The Panel recommends that patients with COVID-19 who require extracorporeal membrane oxygenation (ECMO) or continuous renal replacement therapy or who have thrombosis related to catheters or extracorporeal filters be treated with antithrombotic therapy as per the standard institutional protocols for those without COVID-19 **(AIII)**.

Selection of Anticoagulant or Antiplatelet Drugs

Whenever anticoagulant or antiplatelet therapy is used, potential drug-drug interactions with other concomitant drugs must be considered. The University of Liverpool has collated a list of drug-drug interactions. In hospitalized patients, **LMWH** or **unfractionated heparin** (UFH) is preferred over oral anticoagulants **(AIII)**. Because these types of heparin have shorter half-lives, their effects can be reversed quickly. They can also be administered intravenously or subcutaneously, and they have fewer drug-drug interactions than oral anticoagulants.

Management of Nonhospitalized Patients

ACTIV-4b was a placebo-controlled, randomized trial that evaluated the efficacy of using aspirin or prophylactic doses (2.5 mg) or therapeutic doses (5 mg) of apixaban in outpatients with COVID-19 aged >40 years. After 657 outpatients were randomized, the trial was stopped in June 2021 due to a low event rate for the composite outcome of thromboembolic events, hospitalization, and mortality (1 patient each in the placebo, aspirin, and apixaban 2.5 mg arms and 2 patients in the apixaban 5 mg arm). The median time from randomization to study treatment was 3 days, and 22 participants were hospitalized for COVID-19 prior to initiation of the study drugs.[21]

Two trials evaluated the use of LMWH and its impact on hospitalization and mortality in outpatients with COVID-19. The ETHIC trial was a multicenter, open-label randomized controlled trial of unvaccinated outpatients with COVID-19.[22] Adults with at least 1 risk factor for severe disease were randomized to receive enoxaparin 40 mg subcutaneously (SUBQ) once daily (if they weighed <100 kg) or enoxaparin 40 mg SUBQ twice daily (if they weighed >100 kg) for 21 days or standard of care. The study was terminated early due to a low event rate and slow accrual of participants. There was no difference between the arms in the number of patients who met the composite endpoint of all-cause mortality and all-cause hospitalization (12 of 105 patients [11%] in the enoxaparin arm vs. 12 of 114 patients [11%] in the standard of care arm). Four of the 12 patients in the enoxaparin arm who were

admitted to the hospital required acute medical care or intensive care unit (ICU) admission (3 required mechanical ventilation or ECMO). There were no hospitalizations in the standard of care arm. Bleeding events occurred in 2 patients who received enoxaparin and in 1 patient who received standard of care.

The OVID trial was a multicenter, open-label randomized controlled trial of 472 adults with COVID-19 aged >50 years who were randomized to receive enoxaparin 40 mg SUBQ once daily for 14 days or standard of care.[23] The study was terminated after recruiting 50% of the planned number of participants due to a low probability that enoxaparin would show superiority for the primary outcome. There was no difference between the arms in the number of patients who met the primary composite endpoint of all-cause hospitalization and mortality (8 of 234 patients [3%] in the enoxaparin arm vs. 8 of 238 patients [3%] in the standard of care arm). No major bleeding events occurred during the study.

In nonhospitalized patients with COVID-19, the Panel **recommends against** the use of anticoagulants and antiplatelet therapy (i.e., aspirin, P2Y12 inhibitors) for the prevention of VTE or arterial thrombosis, except in a clinical trial **(AIIa)**. This recommendation does not apply to patients with other indications for antithrombotic therapy.

Management of Hospitalized Patients

Several studies have evaluated the risks and benefits of using prophylactic or therapeutic doses of anticoagulants in patients with COVID-19. Observational studies and clinical trials have examined the effects of anticoagulation on mortality, progression of COVID-19, thrombosis, and bleeding. Some of these studies are outlined below. Observational studies are included here only when evidence from clinical trials is not available.

Prophylactic Dose of Anticoagulation Versus No Anticoagulation—Observational Cohort

An observational study of 4,297 veterans hospitalized with COVID-19 evaluated the benefit of prophylactic anticoagulation. A prophylactic dose of anticoagulation was administered to 3,627 patients with COVID-19 within 24 hours of hospital admission.[24] An inverse probability of treatment weighted analysis showed a cumulative 30-day mortality of 14% among patients who received prophylactic anticoagulation and 19% among patients who were not treated with anticoagulation (HR 0.73; 95% CI, 0.66–0.81). Patients treated with the prophylactic dose did not have a significant difference in the risk of bleeding that required transfusion when compared with patients who were not treated (HR 0.87; 95% CI, 0.71–1.05). Overall, the study demonstrated that patients with COVID-19 may benefit from a prophylactic dose of anticoagulation.

Therapeutic Versus Prophylactic Doses of Heparin in Hospitalized Patients Who Do Not Require Intensive Care Unit-Level Care

Several randomized controlled trials have evaluated the role of therapeutic doses of heparin in reducing the risk of VTE events or mortality in patients hospitalized for COVID-19.

Three open-label randomized controlled trials (the large ATTACC/ACTIV-4a/REMAP-CAP multiplatform trial and the smaller RAPID and HEP-COVID trials) compared therapeutic doses of heparin to prophylactic or intermediate doses of the anticoagulant in selected hospitalized patients who did not require intensive care. Clinical data for these trials are summarized in Table 6a. The inclusion and exclusion criteria for these studies varied, but most included a need for supplemental oxygen and no risk of a major bleeding event. In the larger multiplatform trial, therapeutic doses of heparin increased the number of organ support-free days but did not significantly affect mortality or length of hospitalization when compared with prophylactic doses of heparin.[25]

The RAPID trial enrolled patients with elevated D-dimer levels and hypoxemia. The patients were

randomized to receive therapeutic or prophylactic doses of heparin. There was no statistically significant difference between the arms for the primary endpoint, which was a composite of ICU admission, noninvasive or mechanical ventilation, or death by Day 28. However, the therapeutic dose of heparin reduced the risk of all-cause death, a secondary outcome.[26]

The HEP-COVID trial enrolled patients who required supplemental oxygen and had a D-dimer value >4 times the upper limit of normal (ULN) or a sepsis-induced coagulopathy score of ≥4. There were significantly fewer occurrences of the primary endpoint of VTE, arterial thromboembolism, or all-cause death within 32 days of randomization in the therapeutic LMWH arm than in the prophylactic LMWH arm, but there was no difference between arms for the outcome of death within 32 days.[27]

Given the results of the ATTACC/ACTIV-4a/REMAP-CAP, RAPID, and HEP-COVID trials, for hospitalized, nonpregnant adults with COVID-19 who do not require ICU-level care and have no evidence of VTE:

- The Panel recommends the use of a **therapeutic dose of heparin** for patients with D-dimer levels above the ULN who require low-flow oxygen and who do not have an increased risk of bleeding **(CIIa)**.
  - Contraindications for the use of therapeutic anticoagulation in patients with COVID-19 are a platelet count <50 x 10^9/L, hemoglobin <8 g/dL, the need for dual antiplatelet therapy, bleeding within the past 30 days that required an emergency department visit or hospitalization, a history of a bleeding disorder, or an inherited or active acquired bleeding disorder. This list is based on the exclusion criteria from clinical trials; patients with these conditions have an increased risk of bleeding.
- LMWH is preferred over UFH because of its ease of administration and because LMWH was the predominant form of heparin used in the clinical trials for COVID-19.
- In patients without VTE who have started treatment with therapeutic doses of heparin, treatment should continue for 14 days or until they are transferred to the ICU or discharged from the hospital, whichever comes first.
- Patients with predicted hospitalizations of <72 hours were excluded from the multiplatform ATTACC/ACTIV-4a/REMAP-CAP trial. Whether the benefits of using therapeutic doses of anticoagulation for short hospital stays outweigh the risks is currently unknown.
- The Panel recommends the use of a **prophylactic dose of heparin** for patients who do not meet the criteria for receiving therapeutic heparin or are not receiving a therapeutic dose of heparin for other reasons, unless a contraindication exists **(AIIb)**.
- The Panel **recommends against** the use of a **therapeutic dose of oral anticoagulants** for VTE prophylaxis or the prevention of COVID-19 progression, except in a clinical trial **(AIIa)**.
- There is insufficient evidence for the Panel to recommend either for or against the use of thrombolytic agents for the treatment of COVID-19.

Prophylactic Versus Intermediate or Therapeutic Doses of Heparin in Hospitalized Patients Who Require Intensive Care Unit-Level Care

Several randomized controlled trials have evaluated the role of therapeutic doses of heparin in reducing the incidence of VTE events or mortality in patients in the ICU setting. Clinical data for these trials are summarized in Table 6a.

For the composite endpoint of adjudicated VTE, arterial thrombosis, ECMO, or all-cause mortality, the INSPIRATION trial found no difference between patients in the ICU who were treated with an

intermediate dose of anticoagulation (enoxaparin 1 mg/kg daily) and those who received a prophylactic dose (45.7% vs. 44.1%; OR 1.06; 95% CI, 0.76–1.48). Major bleeding occurred in 2.5% of patients in the intermediate-dose anticoagulation arm and in 1.4% of patients who received the prophylactic dose. Overall, there was no significant benefit of receiving an intermediate dose of anticoagulation for patients with COVID-19 who were in the ICU.[28]

The multiplatform ATTACC/ACTIV-4a/REMAP-CAP trial compared the effectiveness of a therapeutic dose of heparin or LMWH with usual care in reducing the number of organ support-free days among critically ill patients with COVID-19.[25] All 3 trials were stopped for futility. Heparin doses in the usual care arm varied. The median number of organ support-free days was 3 days (IQR -1 to 16) for patients who received a therapeutic dose of anticoagulation and 4 days (IQR -1 to 16) for patients who received usual care. The likelihood of survival to hospital discharge did not differ between the arms (63% for the therapeutic arm vs. 65% for the usual care arm; aOR 0.84; 95% CrI, 0.64–1.11). Major bleeding occurred in 4% of patients who received therapeutic anticoagulation and in 2% of patients who received usual care. Therapeutic doses of heparin showed no significant benefit for patients with COVID-19 who were admitted to the ICU.

The COVID-PACT trial was a multicenter trial with a 2 x 2 factorial design. Critically ill patients with COVID-19 were randomized to receive a therapeutic dose or a prophylactic dose of anticoagulation. They were also randomized to receive either clopidogrel or no antiplatelet therapy.[29] The trial was stopped early because the decreasing number of ICU admissions for patients with COVID-19 made recruitment difficult. Crossover or discontinuation of the assigned treatment occurred in 31% to 37% of patients.

The primary endpoint was a composite of VTE or arterial thrombotic events that occurred by hospital discharge or Day 28. These events included death due to VTE or arterial thrombotic events, pulmonary embolism, clinically evident deep vein thrombosis, myocardial infarction, ischemic stroke, systemic embolic events or acute limb ischemia, and clinically silent deep vein thrombosis. In the on-treatment analysis, the therapeutic dose of anticoagulation was more likely to benefit patients (win ratio 1.95; 95% CI, 1.08–3.55; $P = 0.028$). However, an intention-to-treat analysis and an analysis that only included symptomatic events revealed no statistically significant difference between the arms in the occurrence of the primary endpoint. The use of therapeutic anticoagulation increased the proportion of patients who experienced moderate to severe bleeding events (7.9% in the therapeutic dose arm vs. 0.5% in the prophylactic dose arm; $P = 0.002$). This trial had a high rate of crossover, and the differences between the patients treated with the therapeutic and prophylactic doses of anticoagulation were only found to be statistically significant in the on-treatment analysis. In addition, the use of a therapeutic dose of anticoagulation increased the proportion of patients who experienced bleeding events. These results support the Panel's current recommendation against the use of therapeutic doses of oral anticoagulants to prevent COVID-19 progression.

For hospitalized, nonpregnant adults with COVID-19 who require ICU level-care and who do not have documented or suspected VTE:

- The Panel recommends using a **prophylactic dose of heparin** as VTE prophylaxis, unless a contraindication exists **(AI)**.
- For patients who start on a therapeutic dose of heparin in a non-ICU setting due to COVID-19 and then transfer to the ICU, the Panel recommends switching from the therapeutic dose to a **prophylactic dose of heparin**, unless VTE is confirmed **(BIII)**.
- The Panel **recommends against** the use of an **intermediate dose** (e.g., enoxaparin 1 mg/kg daily) or a **therapeutic dose of anticoagulation** for VTE prophylaxis, except in a clinical trial **(BI)**.

Rivaroxaban Versus Usual Care in Hospitalized Patients With Elevated D-Dimer Levels

The ACTION trial randomized adults who were hospitalized with COVID-19 and elevated D-dimer levels (defined as levels that were above the laboratory ULN) to receive rivaroxaban 20 mg once daily for 30 days or usual care.[30] No statistical difference was found between the arms for the composite endpoint of time to death, hospitalization duration, and oxygen use duration (hierarchical analysis; win ratio 0.86; 95% CI, 0.59–1.22) or for the individual components of the composite endpoint. The probability of clinically relevant, nonmajor bleeding was greater in the rivaroxaban arm (5% in the rivaroxaban arm vs. 1% in the usual care arm; relative risk 5.23; 95% CI, 1.54–17.77), but for major bleeding events, the difference in probability between the arms was not significant (3% in the rivaroxaban arm vs. 1% in the usual care arm; relative risk 2.45; 95% CI, 0.78–7.73).

Given the lack of benefit and the increased risk of bleeding events, the Panel **recommends against** the use of a **therapeutic dose of oral anticoagulants** for VTE prophylaxis or the prevention of COVID-19 progression, except in a clinical trial **(BIIa)**.

Antiplatelet Therapy Versus Usual Care in Hospitalized Patients

Multiple retrospective cohort studies have suggested that the use of aspirin reduced in-hospital mortality in patients who were treated prior to hospital admission or within 24 hours of admission. These studies have been summarized in meta-analyses.[31-34] These epidemiologic studies used propensity scoring or adjusted for potential confounders, but indication bias cannot be fully removed from these studies. Thus, randomized controlled trials are needed to further define the role of aspirin and other antiplatelet therapies as adjunctive treatments in the management of COVID-19.

The RECOVERY trial randomized hospitalized adults with COVID-19 to receive usual care plus aspirin 150 mg per day (n = 7,351) or usual care only (n = 7,541).[35] At enrollment, 38% of the patients required noninvasive ventilation or mechanical ventilation. Mortality at 28 days was 17% in both arms (rate ratio 0.96; 95% CI, 0.89–1.04). Among patients who were not receiving mechanical ventilation at baseline, there was no difference between the arms in the proportion of patients who progressed to requiring mechanical ventilation or death (21% in the aspirin arm vs. 22% in the usual care arm; rate ratio 0.96; 95% CI, 0.90–1.03). Among those treated with aspirin, the incidence of thrombotic events was lower (4.6% vs. 5.3%; absolute difference 0.6%; SE 0.4%), and the incidence of major bleeding events was higher (1.6% vs. 1.0%; absolute difference 0.6%; SE 0.2%). Overall, in this large trial of hospitalized patients with COVID-19, the use of aspirin was associated with an increase in the incidence of major bleeding events and did not reduce the risk of death.

The ACTIV-4a trial compared the use of P2Y12 inhibitor therapy plus a therapeutic dose of heparin to a therapeutic dose of heparin alone in hospitalized patients with COVID-19. In this study, enrollment of noncritically ill patients was stopped early due to futility; the combination therapy did not increase the number of organ support-free days.[36] The limitations of this study include the open-label design, the use of different P2Y12 inhibitors, and the trial size.

Based on the findings of the ACTIV-4a and RECOVERY trials, the Panel **recommends against** the use of antiplatelet therapy to prevent COVID-19 progression or death in noncritically ill patients **(BIIa)**.

The REMAP-CAP study team randomized critically ill patients with COVID-19 to receive aspirin (n = 565), a P2Y12 inhibitor (n = 455), or no antiplatelet therapy (n = 529).[37] Treatment continued for 14 days or until hospital discharge, whichever came first. The aspirin and P2Y12 inhibitor arms were pooled for analysis because the criteria for equivalence were met. The trial was stopped early due to futility, as the median number of organ support-free days did not differ between the pooled antiplatelet arm and the control arm (7 days; IQR 1–16 days; 95.7% posterior probability of futility). There was no statistically significant difference between the arms in the number of patients who survived to hospital

discharge (723 of 1,011 patients [71.5%] in the pooled antiplatelet arm vs. 354 of 521 patients [67.9%] in the control arm; median-adjusted OR 1.27; 95% CrI, 0.99–1.62). The pooled antiplatelet arm had improved survival by 90 days (median aHR 1.22; 95% CrI, 1.06–1.40). The use of antiplatelet therapy was associated with an increased incidence of major bleeding (2.1% in the pooled antiplatelet arm vs. 0.4% in the control arm; aOR 2.97; 95% CrI, 1.23–8.28; adjusted absolute risk difference of 0.8%; 95% CrI, 0.1% to 2.7%).

In the RECOVERY trial, the use of aspirin therapy was not associated with a reduction in mortality in the subgroups of patients who required noninvasive ventilation or mechanical ventilation at baseline. In the REMAP-CAP trial, administering antiplatelet therapy to critically ill patients with COVID-19 improved 90-day survival but did not increase the number of organ support-free days. In both studies, the use of antiplatelet therapy was associated with an increased risk of bleeding. The COVID-PACT trial randomized 292 adult patients with COVID-19 who required ICU-level care to receive either clopidogrel or no antiplatelet therapy.[29] No differences occurred between the arms in the incidence of VTE, arterial thrombotic events, or bleeding. Given the inconsistent results of these trials, there is insufficient evidence for the Panel to recommend either for or against the use of antiplatelet therapy in critically ill patients with COVID-19. Eligible patients should be encouraged to participate in clinical trials that are evaluating the use of antiplatelet therapy.

The clinical data for the trials discussed above are summarized in Table 6b.

Thrombolytic Therapy

Clinical trials are evaluating the effects of thrombolysis on mortality and the progression of COVID-19. There is insufficient evidence for the Panel to recommend either for or against the use of thrombolytic agents for VTE prophylaxis in hospitalized patients with COVID-19 outside of a clinical trial.

Patients Discharged From the Hospital

For patients with a high risk of VTE who do not have COVID-19, post-discharge prophylaxis has been shown to be beneficial. The Food and Drug Administration approved the use of rivaroxaban 10 mg once daily for 31 to 39 days in these patients.[38,39] Inclusion criteria for the trials that studied post-discharge VTE prophylaxis included:

- A VTE risk score of ≥4 on the modified International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) tool;[40] *or*
- A VTE risk score ≥2 on the modified IMPROVE tool[41] and a D-dimer level >2 times ULN.[38]

The MICHELLE trial randomized 320 patients with COVID-19 and an IMPROVE score of ≥4 or 2 to 3 with a D-dimer level >500 ng/mL to receive rivaroxaban 10 mg orally once daily or no anticoagulation for 35 days.[42] The primary outcome was a composite of symptomatic VTE, fatal pulmonary embolism, symptomatic arterial thromboembolism, cardiovascular death, or asymptomatic VTE detected on screening imaging at Day 35. Five patients (3%) who were treated with rivaroxaban and 15 patients (9%) who did not receive anticoagulation experienced a thrombotic event (relative risk 0.33; 95% CI, 0.13–0.9). One patient who received rivaroxaban and 10 patients who did not receive anticoagulation experienced symptomatic events. No major bleeding events occurred, and 2 patients had clinically relevant, nonmajor bleeding in each arm. The open-label design and the inclusion of asymptomatic events that were detected on screening ultrasounds and computed tomography scans may have biased the results. Additionally, two-thirds of the screened patients did not meet the eligibility criteria for the trial, which limits the generalizability of the results.

The Panel **recommends against** routinely continuing VTE prophylaxis for patients with COVID-19

after hospital discharge unless they have another indication or are participating in a clinical trial **(AIII)**. For patients who are at high risk of VTE and low risk of bleeding, there is insufficient evidence for the Panel to recommend either for or against continuing anticoagulation after discharge, unless another indication for VTE prophylaxis exists. Decisions to use post-discharge VTE prophylaxis in patients with COVID-19 should include consideration of the individual patient's risk factors for VTE, bleeding risks, and feasibility. Eligible patients should be encouraged to participate in clinical trials that are evaluating the use of VTE prophylaxis.

Children With COVID-19 or MIS-C

For the Panel's recommendations on the use of antithrombotic therapy in children, see Therapeutic Management of Hospitalized Children With COVID-19 and Therapeutic Management of Hospitalized Pediatric Patients With Multisystem Inflammatory Syndrome in Children (MIS-C) (With Discussion on Multisystem Inflammatory Syndrome in Adults [MIS-A]).

Pregnant and Lactating Patients

Because pregnancy is a hypercoagulable state, the risk of thromboembolism is greater in pregnant individuals than in nonpregnant individuals.[43] 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.[44-46] The American College of Obstetricians and Gynecologists (ACOG) advises that although there are not enough data to recommend either for or against the use of thromboprophylaxis, in the setting of COVID-19 during pregnancy, VTE prophylaxis can reasonably be considered for pregnant individuals hospitalized with COVID-19, particularly for those who have severe disease.[47] If there are no contraindications, the Society for Maternal-Fetal Medicine recommends the use of prophylactic heparin or LMWH in pregnant patients who are critically ill or receiving mechanical ventilation.[48] 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.[49,50] If delivery is imminent, or if there are other risks for bleeding, the risk of bleeding may outweigh the potential benefit of using VTE prophylaxis in pregnant individuals.

Outside of pregnancy, D-dimer levels have been used to stratify VTE risk. However, physiologic increases in D-dimer levels may occur during pregnancy, making elevated D-dimer values an unreliable predictor that should not be used to evaluate VTE risk during pregnancy in the setting of COVID-19.[51-53]

In general, the preferred anticoagulants for use during pregnancy are heparin compounds. Because of its reliability and ease of administration, LMWH is recommended rather than UFH for the prevention and treatment of VTE in pregnancy.[50] Direct-acting anticoagulants are not routinely recommended for use during pregnancy because of a lack of safety data for pregnant individuals.[49] The use of warfarin to prevent or treat VTE should be avoided in pregnant individuals regardless of their COVID-19 status, especially during the first trimester, due to the concern for teratogenicity.

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

- The Panel recommends that pregnant patients who are receiving anticoagulant or antiplatelet therapies for underlying conditions continue these medications after they receive a diagnosis of COVID-19 **(AIII)**.
- The Panel recommends the use of a **prophylactic dose of anticoagulation** for pregnant patients who are hospitalized for manifestations of COVID-19, unless a contraindication exists **(BIII)**.

- Because pregnant patients have not been included in most clinical trials evaluating therapeutic anticoagulation in the setting of COVID-19, there is insufficient evidence for the Panel to recommend either for or against the use of therapeutic anticoagulation in pregnant patients with COVID-19 who do not have evidence of VTE.
- As in nonpregnant patients, VTE prophylaxis after hospital discharge is not routinely recommended for pregnant patients **(BIII)**. Decisions to continue VTE prophylaxis in the pregnant or postpartum patient after discharge should be individualized, with consideration of concomitant VTE risk factors.
- The use of anticoagulation therapy during labor and delivery requires specialized care and planning. The management of anticoagulation therapy in pregnant patients with COVID-19 should be similar to the management used for pregnant patients with other conditions **(AIII)**.
- UFH, LMWH, and warfarin do not accumulate in breast milk and do not induce an anticoagulant effect in the newborn; therefore, they can be used by breastfeeding individuals who require VTE prophylaxis or treatment **(AIII)**.

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Table 6a. Anticoagulant Therapy: Selected Clinical Data

Last Updated: September 26, 2022

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

Methods	Results	Limitations and Interpretation
ATTACC/ACTIV-4a/REMAP-CAP: Multiplatform, Open-Label RCT of Therapeutic Anticoagulation in Noncritically Ill, Hospitalized Patients With COVID-19 in 9 Countries[1]		

Key Inclusion Criteria
• Hospitalized with laboratory-confirmed SARS-CoV-2 infection without need for HFNC oxygen, NIV, MV, vasopressors, or inotropes
Key Exclusion Criteria
• Discharge expected ≤72 hours
• Requirement for therapeutic anticoagulation or dual antiplatelet therapy
• High bleeding risk
Interventions
• Therapeutic UFH or LMWH for 14 days or until discharge, whichever comes first (n = 1,190)
• SOC (n = 1,054)
Primary Endpoint
• Organ support-free days at Day 21, evaluated on an ordinal scale
Key Secondary Endpoints
• Survival until hospital discharge
• Hospital LOS
• Thrombosis or major bleeding
	Participant Characteristics
	• Median age 59 years; 59% men; median BMI 30
	• 52% with HTN; 30% with DM; 11% with CVD
	• 66% required low-flow oxygen
	• D-dimer:
	  • 48.4% <2 times ULN
	  • 28.4% ≥2 times ULN
	  • 23.1% unknown
	• 62% on corticosteroids; 36% on RDV
	Primary Outcomes
	• Organ support-free days: therapeutic anticoagulation superior to SOC (aOR 1.27; 95% CrI, 1.03–1.58; 99% posterior probability)
	• Survival until hospital discharge without organ support: 4% absolute difference favoring therapeutic anticoagulation arm (95% CrI, 0.5–7.2)
	• Outcome consistent across D-dimer stratum
	Secondary Outcomes
	• Survival until hospital discharge: 92% in both arms
	• Hospital LOS: no difference between arms (aOR 1.03; 95% CrI, 0.94–1.13)
	• Thrombosis: 1% in therapeutic arm vs. 2% in SOC arm
	• Major bleeding: 2% in therapeutic arm vs. 1% in SOC arm
		Key Limitations
		• Open-label study
		• Anticoagulation dose varied in SOC arm (27% received intermediate-dose thromboprophylaxis).
		• Studies had different criteria for ICU care and expected hospital LOS.
		• Only enrolled 17% of screened patients
		Interpretation
		• Therapeutic heparin increased organ support-free days and decreased the number of patients requiring organ support.
		• Therapeutic heparin did not significantly affect hospital LOS or the number of major thrombosis events or deaths.
		• Major bleeds occurred 1% more frequently in therapeutic arm than in SOC arm.

Methods	Results	Limitations and Interpretation
RAPID: Open-Label RCT of Therapeutic Heparin in Moderately Ill, Hospitalized Patients With COVID-19 in 6 Countries[2]		

Key Inclusion Criteria
• Hospitalized with COVID-19 and D-dimer ≥2 times ULN or any elevated D-dimer level and SpO_2 ≤93% on room air
• Hospitalized <5 days
Key Exclusion Criteria
• Indication for therapeutic anticoagulation
• Dual antiplatelet therapy
• High bleeding risk
Interventions
• Therapeutic UFH or LMWH for 28 days or until discharge or death (n = 228)
• Prophylactic UFH or LMWH for 28 days or until discharge or death (n = 237)
Primary Endpoint
• Composite of ICU admission, NIV or MV, or death up to 28 days
Key Secondary Endpoints
• All-cause death
• Mean organ support-free days
• VTE
• Major bleeding event
• Mean hospital-free days alive
	Participant Characteristics
	• Median age 60 years; 57% men; mean BMI 30
	• 48% with HTN; 34% with DM; 7% with CVD
	• 91% had hypoxia; 6% received HFNC oxygen
	• D-dimer:
	  • 49% <2 times ULN
	  • 51% ≥2 times ULN
	• 69% on corticosteroids
	Primary Outcome
	• ICU admission, NIV or MV, or death: 16% in therapeutic arm vs. 22% in prophylactic arm (OR 0.69; 95% CI, 0.43–1.10)
	Secondary Outcomes
	• All-cause death: 2% in therapeutic arm vs. 8% in prophylactic arm (OR 0.22; 95% CI, 0.07–0.65)
	• Mean organ support-free days: 26 days in therapeutic arm vs. 24 days in prophylactic arm (OR 1.41; 95% CI, 0.9–2.21)
	• No difference between arms for VTE (1% in therapeutic arm vs. 3% in prophylactic arm) or major bleeding (1% in therapeutic arm vs. 2% in prophylactic arm)
	• Mean hospital-free days alive: 20 days in therapeutic arm vs. 18 days in prophylactic arm (OR 1.09; 95% CI, 0.79–1.50)
		Key Limitations
		• Open-label study
		• Only enrolled 12% of screened patients
		Interpretation
		• Compared to prophylactic heparin, therapeutic heparin reduced mortality (a secondary endpoint) but had no effects on the composite primary endpoint of ICU admission, the need for NIV or MV, or death up to 28 days.
		• There were no differences between the arms in the proportions of patients who experienced major bleeding events or VTE.

Methods	Results	Limitations and Interpretation
HEP-COVID: Open-Label RCT of Therapeutic Heparin in High-Risk, Hospitalized Patients With COVID-19 in the United States[3]		

Key Inclusion Criteria
• Hospitalized with supplemental oxygen
• D-dimer >4 times ULN or sepsis-induced coagulopathy score of ≥4
• Hospitalized <72 hours
Key Exclusion Criteria
• Indication for therapeutic anticoagulation
• Dual antiplatelet therapy
• High bleeding risk
• CrCl <15 mL/min
Interventions
• Therapeutic LMWH until hospital discharge or primary endpoint met (n = 129)
• Usual care of prophylactic or intermediate-dose LMWH until hospital discharge or primary endpoint met (n = 124)
Primary Endpoint
• Composite of VTE, ATE, or death of any cause within 32 days of randomization
Key Safety Endpoint
• Major bleeding
	Participant Characteristics
	• Median age 67 years; 54% men; mean BMI 30
	• 60% with HTN; 37% with DM; 75 with CVD
	• 64% received oxygen via nasal cannula; 15% received high-flow oxygen or NIV; 5% received MV
	• 80% on corticosteroids
	Primary Outcomes
	• Composite of VTE, ATE, and death within 32 days: 29% in therapeutic arm vs. 42% in usual care arm (relative risk 0.68; 95% CI, 0.49–0.96)
	  • Death: 19% in therapeutic arm vs. 25% in usual care arm (relative risk 0.78; 95% CI, 0.49–1.23)
	  • Thrombotic events: 11% in therapeutic arm vs. 29% in usual care arm (relative risk 0.37; 95% CI, 0.21–0.66)
	• Non-ICU stratum composite of VTE, ATE, or death within 32 days: 17% in therapeutic arm vs. 36% in usual care arm (relative risk 0.46; 95% CI, 0.27–0.81)
	Key Safety Outcomes
	• Major bleeding: 5% in therapeutic arm vs. 2% in usual care arm (relative risk 2.88, 95% CI, 0.59–14.02)
	  • Non-ICU stratum major bleeding: 2% in both arms
		Key Limitations
		• Open-label study
		• Only enrolled 2% of screened patients
		Interpretation
		• Compared to usual care, therapeutic LMWH reduced the incidence of VTE, ATE, and death.
		• For patients not in the ICU, therapeutic LMWH significantly reduced thrombotic events and did not increase major bleeding.

Methods	Results	Limitations and Interpretation
ACTION: Open-Label RCT of Therapeutic Oral Anticoagulation (Rivaroxaban) in Hospitalized Patients With COVID-19 in Brazil[4]		

Key Inclusion Criteria
• Hospitalized for COVID-19 with elevated D-dimer level
• Symptoms for ≤14 days
Key Exclusion Criteria
• Indication for therapeutic anticoagulation
• CrCl <30 mL/min
• P2Y12 inhibitor therapy or aspirin >100 mg
• High bleeding risk
Interventions
• Therapeutic anticoagulation for 30 days: rivaroxaban 15 mg or 20 mg daily; if clinically unstable, enoxaparin 1 mg/kg twice daily or UFH (n = 311)
• Usual care prophylactic anticoagulation with enoxaparin or UFH during hospitalization (n = 304)
Primary Endpoint
• Hierarchical composite of time to death, hospital duration, and oxygen use duration through Day 30
Key Secondary Endpoints
• Thrombosis, with and without all-cause death
• Mortality
• Bleeding events
	Participant Characteristics
	• Median age 57 years; 60% men; mean BMI 30
	• 49% with HTN; 24% with DM; 5% with coronary disease
	• Critically ill: 7% in therapeutic arm; 5% in usual care arm
	• 75% required oxygen: 60% low-flow oxygen; 8% HFNC oxygen; 1% NIV; 6% MV
	• 83% on corticosteroids
	Primary Outcomes
	• Composite of time to death, hospital duration, and oxygen use duration: no difference between arms (win ratio 0.86; 95% CI, 0.59–1.22)
	Secondary Outcomes
	• No difference between therapeutic and prophylactic arms:
	  • Mortality: 11% vs. 8%
	  • Thrombosis: 7% vs. 10%
	• Any bleeding: 12% in therapeutic arm vs. 3% in usual care arm
	• Major bleeding: 3% in therapeutic arm vs. 1% in usual care arm
	• Clinically relevant, nonmajor bleeding: 5% in therapeutic arm vs. 1% in usual care arm
		Key Limitations
		• Open-label study
		• Only enrolled 18% of screened patients
		• Longer duration of anticoagulation in the rivaroxaban arm (30 days) than the prophylactic anticoagulation arm (mean duration of 8 days)
		Interpretation
		• When compared with usual care, therapeutic rivaroxaban did not reduce mortality, hospital duration, oxygen use duration, or thrombosis.
		• Patients who received therapeutic rivaroxaban had more clinically relevant nonmajor bleeding than those who received usual care.
		• The longer duration of therapy in the rivaroxaban arm may have influenced the difference in bleeding events.

Methods	Results	Limitations and Interpretation
REMAP-CAP/ACTIV-4a/ATTACC: Multiplatform, Open-Label RCT of Therapeutic Anticoagulation in Critically Ill, Hospitalized Patients With COVID-19 in 20 Countries[5]		

Key Inclusion Criteria
• Hospitalized with severe COVID-19 and receiving HFNC oxygen, NIV, MV, ECMO, vasopressors, or inotropes
• Hospitalized <72 hours (ACTIV-4a, ATTACC) or <14 days (REMAP-CAP)
Key Exclusion Criteria
• Discharge expected within 72 hours
• Requirement for therapeutic anticoagulation or dual antiplatelet therapy
• High bleeding risk
Interventions
• Therapeutic UFH or LMWH for 14 days or until discharge, whichever comes first (n = 534)
• Usual care (n = 564)
Primary Endpoint
• Organ support-free days at Day 21
Key Secondary Endpoints
• Survival to hospital discharge
• Any thrombosis
• Composite of major thrombotic events or death
• Bleeding events
	Participant Characteristics
	• Median age 60 years; 70% men; median BMI 30
	• 24% with chronic respiratory disease; 33% with DM; 10% with chronic kidney disease; 8% with severe CVD
	• 32% required HFNC oxygen; 38% required NIV; 29% required MV
	• 18% on vasopressors; 82% on corticosteroids; 32% on RDV
	Primary Outcome
	• Median organ support-free days at Day 21: 4 days in therapeutic arm vs. 5 days in usual care arm (aOR 0.83; 95% CrI, 0.67–1.03; 99.9% posterior probability of futility; OR < 1.2)
	Secondary Outcomes
	• No difference between therapeutic and usual care arms:
	  • Survival to hospital discharge: 63% vs. 65% (aOR 0.84; 95% CrI, 0.64–1.11)
	  • Thrombosis: 6% vs. 10%
	  • Major thrombotic events or death: 41% both arms
	  • Major bleeding events: 4% vs. 2% (aOR 1.48; 95% CrI, 0.75–3.04)
		Key Limitations
		• Open-label study
		• Anticoagulation dose varied in usual care arm (i.e., 51% intermediate, 2% subtherapeutic, 5% therapeutic).
		• Inclusion criteria for hospital LOS and ICU-level care differed across trials.
		• Trial stopped for futility.
		Interpretation
		• In patients requiring ICU care, therapeutic heparin did not reduce the duration of organ support or mortality.
		• Although the differences were nonsignificant, patients who received therapeutic anticoagulation had more bleeding events and fewer thrombotic events than patients who received usual care.

Methods	Results	Limitations and Interpretation
INSPIRATION: Open-Label RCT of Intermediate-Dose Versus Prophylactic-Dose Anticoagulant in Patients in Intensive Care With COVID-19 in Iran[6]		

Key Inclusion Criteria
• Admitted to ICU
• Hospitalized <7 days
Key Exclusion Criteria
• Life expectancy <24 hours
• Indication for therapeutic anticoagulation
• Overt bleeding
Interventions
• Intermediate-dose anticoagulation: enoxaparin 1 mg/kg daily (n = 276)
• Prophylactic-dose anticoagulation (n = 286)
Primary Endpoint
• Composite of adjudicated acute VTE, ATE, ECMO, or all-cause mortality within 30 days
Key Secondary Endpoints
• All-cause mortality
• VTE
• Bleeding event
	Participant Characteristics
	• Median age 62 years; 58% men; median BMI 27
	• 44% with HTN; 28% with DM; 14% with coronary artery disease
	• 32% required NIV; 20% required MV
	• 23% on vasopressors; 93% on corticosteroids; 60% on RDV
	Primary Outcome
	• Composite of adjudicated acute VTE, ATE, ECMO, or all-cause mortality: 46% in therapeutic arm vs. 44% in prophylactic arm (OR 1.06; 95% CI, 0.76–1.48)
	Secondary Outcomes
	• No difference between therapeutic and prophylactic arms:
	  • All-cause mortality: 43% vs. 41%
	  • VTE: 3% both arms
	  • Major bleeding and clinically relevant nonmajor bleeding: 6.3% vs. 3.1% (OR 2.02; 95% CI, 0.89–4.61)
		Key Limitations
		• Open-label study
		• Not all patients received ICU-level care.
		Interpretation
		• Intermediate-dose anticoagulation did not significantly reduce VTE and ATE, the need for ECMO, or mortality.
		• Although the difference was nonsignificant, patients who received intermediate-dose anticoagulation had more bleeding events than patients who received usual care.

Methods	Results	Limitations and Interpretation
OVID: Open-Label RCT of Low-Molecular-Weight Heparin for Thromboprophylaxis in Symptomatic, Nonhospitalized Patients With COVID-19 in Germany and Switzerland[7]		
Key Inclusion Criteria • Aged ≥50 years • Positive SARS-CoV-2 test result within past 5 days • Respiratory symptoms or temperature ≥37.5°C **Key Exclusion Criteria** • Severe renal or hepatic dysfunction • Severe anemia or recent major bleeding • Receiving dual antiplatelet treatment **Interventions** • Enoxaparin 40 mg SUBQ once daily for 14 days (n = 234) • SOC (n = 238) **Primary Endpoint** • Composite of any untoward hospitalization and all-cause death by Day 30 **Key Secondary Endpoints** • Composite of major arterial and venous cardiovascular events by Day 30 • Occurrence of bleeding events	**Participant Characteristics** • Median age 57 years; 46% women; 96% White • Median time from COVID-19 diagnosis to randomization: 3 days • 24% with HTN; 8% with DM; 5% with CVD • 9.5% received at least 1 dose of a COVID-19 vaccine **Primary Outcome** • Composite of any untoward hospitalization and all-cause death by Day 30: 8 (3%) in enoxaparin arm vs. 8 (3%) in SOC arm (adjusted relative risk 0.98; 95% CI, 0.37–2.56; $P = 0.96$) **Key Secondary Outcomes** • Composite of major arterial and venous cardiovascular events at 30 days: 2 (1%) in enoxaparin arm vs. 4 (2%) in SOC arm (relative risk 0.51; 95% CI, 0.09–2.74) • No major or clinically relevant nonmajor bleeding events occurred	**Key Limitations** • Open-label study • Study terminated early because of the very low probability that enoxaparin would show superiority for the primary outcome. **Interpretation** • Thromboprophylaxis with enoxaparin did not reduce the risk of hospitalization or death among nonhospitalized, symptomatic patients with COVID-19.

Methods	Results	Limitations and Interpretation
ETHIC: Open-Label RCT of Low-Molecular-Weight Heparin for Thromboprophylaxis in Symptomatic Outpatients With COVID-19 in Belgium, Brazil, India, South Africa, Spain, and the UK[8]		
Key Inclusion Criteria • Aged ≥30 years • RT-PCR-confirmed SARS-CoV-2 infection, with symptoms for ≤9 days • ≥1 risk factor for severe disease **Key Exclusion Criteria** • Receipt of COVID-19 vaccination • eGFR <30 mL/min • Receiving anticoagulant or antiplatelet therapy, except low-dose aspirin **Interventions** • Enoxaparin 40 mg SUBQ daily (for patients weighing <100 kg) or enoxaparin 40 mg SUBQ twice daily (for patients weighing ≥100 kg), self-administered for 21 days (n = 105) • SOC (n = 114) **Primary Endpoint** • Composite of all-cause hospitalization and all-cause mortality by Day 21 **Key Secondary Endpoints** • VTE by Days 21, 50, and 90 • Bleeding events by Days 21 and 50	**Participant Characteristics** • Median age 59 years; 56% men • Median time from first symptom to randomization: 5 days **Primary Outcomes** • Composite of all-cause hospitalization and all-cause mortality by Day 21: 12 (11%) in enoxaparin arm vs. 12 (11%) in SOC arm (HR 1.09; 95% CI, 0.49–2.43; *P* = 0.83) • Patients who required hospitalization: 12 in enoxaparin arm vs. 12 in SOC arm • Hospitalized patients who required acute medical care or ICU admission: 4 in enoxaparin arm vs. 0 in SOC arm **Key Secondary Outcomes** • VTE by Day 90: 1 (1%) in enoxaparin arm vs. 2 (2%) in SOC arm • Bleeding events by Day 50: 2 (2%) in enoxaparin arm vs. 2 (2%) in SOC arm	**Key Limitations** • Open-label study • Study terminated early because of low event rate and lack of efficacy. **Interpretation** • This study demonstrated no benefit of prophylaxis with LMWH in outpatients with COVID-19 who were at risk of progressing to severe disease.

Key: ATE = arterial thromboembolism; BMI = body mass index; CrCl = creatinine clearance; CVD = cardiovascular disease; DM = diabetes mellitus; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; HFNC = high-flow nasal cannula; HTN = hypertension; ICU = intensive care unit; LMWH = low-molecular-weight heparin; LOS = length of stay; MV = mechanical ventilation; NIV = noninvasive ventilation; the Panel = the COVID-19 Treatment Guidelines Panel; RCT = randomized controlled trial; RDV = remdesivir; RT-PCR = reverse transcriptase polymerase chain reaction; SOC = standard of care; SpO_2 = oxygen saturation; SUBQ = subcutaneously; UFH = unfractionated heparin; ULN = upper limit of normal; VTE = venous thromboembolism

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Table 6b. Antiplatelet Therapy: Selected Clinical Data

Last Updated: December 1, 2022

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

Methods	Results	Limitations and Interpretation
ACTIV-4a: Open-Label, Adaptive RCT of Adding a P2Y12 Inhibitor to Anticoagulant Therapy in Noncritically Ill Hospitalized Patients With COVID-19 in Brazil, Italy, Spain, and the United States[1]		

Key Inclusion Criteria
• Laboratory-confirmed SARS-CoV-2 infection
• Any 1 of the following:
  • D-dimer level ≥2 times ULN
  • Aged 60–84 years
  • Aged <60 years with oxygen requirement >2 L/min, HTN, DM, eGFR <60 mL/min, CVD, or BMI ≥35
Key Exclusion Criteria
• Required HFNC oxygen ≥20 L/min, NIV, MV, ECMO, vasopressors, or inotropes
• >72 hours since hospital admission
Interventions
• Therapeutic dose of heparin plus P2Y12 inhibitor for 14 days or until discharge (n = 293)
• Therapeutic dose of heparin (usual care arm) (n = 269)
Primary Endpoints
• Number of organ support-free days by Day 21
• Major bleeding event by Day 28
Key Secondary Endpoint
• Major thrombotic event or death by Day 28
	Participant Characteristics
	• Mean age 53 years; 42% women; 62% White
	• HTN: 43% in P2Y12 inhibitor arm vs. 55% in usual care arm
	• 65% on glucocorticoids; 52% on RDV; 3% on IL-6 inhibitors; 14% on aspirin
	• Median duration of P2Y12 inhibitor treatment: 6 days
	  • 63% received ticagrelor; 37% received clopidogrel
	Primary Outcomes
	• Median number of organ support-free days by Day 21: 21 in both arms (aOR 0.83; 95% CrI, 0.55–1.25; posterior probability of futility 96%)
	• Major bleeding events by Day 28: 2.0% in P2Y12 inhibitor arm vs. 0.7% in usual care arm (aOR 3.31; 95% CI, 0.64–17.2; $P = 0.15$)
	Secondary Outcome
	• Major thrombotic event or death by Day 28: 6.1% in P2Y12 inhibitor arm vs. 4.5% in usual care arm (aOR 1.42; 95% CI, 0.64–3.13)
		Key Limitations
		• Open-label study
		• Study stopped early for futility
		• Different P2Y12 inhibitors used
		• Median duration of P2Y12 inhibitor use was 6 days, which may not be sufficient to observe effects.
		Interpretation
		• Among hospitalized patients with COVID-19 who were not critically ill, adding a P2Y12 inhibitor to a therapeutic dose of heparin did not increase the number of organ support-free days.
		• Major bleeding events occurred infrequently during the study. The number of patients who experienced a major bleeding event was not significantly different between the arms.

Methods	Results	Limitations and Interpretation
RECOVERY: Open-Label RCT of Aspirin in Hospitalized Patients With COVID-19 in Indonesia, Nepal, and the United Kingdom[2]		

Key Inclusion Criterion
• Clinically suspected or laboratory-confirmed SARS-CoV-2 infection
Key Exclusion Criteria
• Hypersensitivity to aspirin
• Recent history of major bleeding events
• Currently receiving aspirin or another antiplatelet treatment
Interventions
• Aspirin 150 mg once daily until discharge (n = 7,351)
• SOC alone (n = 7,541)
Primary Endpoint
• All-cause mortality at 28 days
Key Secondary Endpoints
• Progression to MV or death at 28 days
• Major bleeding or thrombotic events at 28 days
	Participant Characteristics
	• Mean age 59 years; 62% men; 75% White
	• 97% had laboratory-confirmed SARS-CoV-2 infection
	• At baseline:
	  • 33% on NIV or MV
	  • 34% on intermediate- or therapeutic-dose LMWH
	  • 60% on standard-dose LMWH
	  • 7% received no thromboprophylaxis
	• 94% on corticosteroids; 26% on RDV; 13% on tocilizumab; 6% on baricitinib
	Primary Outcome
	• All-cause mortality at 28 days: 17% in both arms (rate ratio 0.96; 95% CI, 0.89–1.04; $P = 0.35$)
	Secondary Outcomes
	• Progression to MV or death at 28 days: 21% in aspirin arm vs. 22% in SOC arm (risk ratio 0.96; 95% CI, 0.90–1.03)
	• Major bleeding events at 28 days: 1.6% in aspirin arm vs. 1.0% in SOC arm ($P = 0.0028$)
	• Thrombotic events at 28 days: 4.6% in aspirin arm vs. 5.3% in SOC arm ($P = 0.07$)
		Key Limitation
		• Because of open-label design, reporting of thrombotic and major bleeding events may have influenced treatment allocation.
		Interpretation
		• In hospitalized patients with COVID-19, the use of aspirin was not associated with reductions in 28-day mortality or the risk of progressing to MV or death.

Methods	Results	Limitations and Interpretation
REMAP-CAP: Open-Label, Adaptive RCT of Antiplatelet Therapy in Critically Ill Patients With COVID-19 in 8 Countries in Europe and Asia[3]		

Key Inclusion Criteria
• Clinically suspected or laboratory-confirmed SARS-CoV-2 infection
• Within 48 hours of ICU admission
Key Exclusion Criteria
• Bleeding risk sufficient to contraindicate antiplatelet therapy
• CrCl <30 mL/min
• Receiving antiplatelet therapy or NSAID
Interventions
• 1 of the following plus anticoagulation for 14 days or until hospital discharge, whichever came first:
  • Aspirin 75–100 mg once daily (n = 565)
  • P2Y12 inhibitor (n = 455)
  • No antiplatelet therapy (control arm) (n = 529)
Primary Endpoint
• Number of organ support-free days by Day 21
Key Secondary Endpoints
• Survival to hospital discharge
• Survival to Day 90
• Major bleeding event by Day 14
	Participant Characteristics
	• Mean age 57 years; 34% women; 77% White
	• At baseline, 98% on LMWH:
	  • 19% on low-dose LMWH
	  • 59% on intermediate-dose LMWH
	  • 12% on therapeutic-dose LMWH
	• 98% on steroids; 21% on RDV; 44% on tocilizumab; 11% on sarilumab
	• In P2Y12 inhibitor arm, 88.5% received clopidogrel, 1.3% received ticagrelor, 1.3% received prasugrel, and 8.8% received an unknown P2Y12 inhibitor
	Primary Outcome
	• Data from aspirin and P2Y12 inhibitor arms were pooled and reported as "pooled antiplatelet arm" in final analysis:
	  • Median number of organ support-free days by Day 21: 7 in pooled antiplatelet arm and control arm (aOR 1.02; 95% CrI, 0.86–1.23; posterior probability of futility 96%)
	Secondary Outcomes
	• Survival to hospital discharge: 71.5% in pooled antiplatelet arm vs. 67.9% in control arm (median-adjusted OR 1.27; 95% CrI, 0.99–1.62; adjusted absolute difference 5%; 95% CrI, -0.2% to 9.5%; 97% posterior probability of efficacy)
	• Survival to Day 90: 72% in pooled antiplatelet arm vs. 68% in control arm (HR with pooled antiplatelets 1.22; 95% CrI, 1.06–1.40; 99.7% posterior probability of efficacy)
	• Major bleeding event by Day 14: 2.1% in pooled antiplatelet arm vs. 0.4% in control arm (aOR 2.97; 95% CrI, 1.23–8.28; posterior probability of harm 99.4%)
		Key Limitations
		• Open-label study
		• Different P2Y12 inhibitors used
		• Trial stopped for futility. Because equivalence for aspirin and P2Y12 inhibitor arms was reached, these arms were pooled for analyses.
		Interpretation
		• In critically ill patients with COVID-19, the use of aspirin or a P2Y12 inhibitor did not reduce the number of organ support-free days or in-hospital mortality.
		• Patients in the pooled antiplatelet arm had more major bleeding events than those in the control arm, but they had improved survival over 90 days.

Methods	Results	Limitations and Interpretation
COVID-PACT: Open-Label RCT of Clopidogrel in Adults With COVID-19 Who Were Receiving ICU-Level Care in the United States[4]		
Key Inclusion Criteria • Aged ≥18 years • Acute SARS-CoV-2 infection • Required ICU-level care for ≤96 hours prior to randomization **Key Exclusion Criteria** • Ongoing or planned use of a therapeutic dose of anticoagulation or dual antiplatelet therapy • High risk of bleeding • History of HIT • Ischemic stroke within 2 weeks **Interventions** • Clopidogrel 300 mg at randomization, then clopidogrel 75 mg once daily until hospital discharge or Day 28, whichever came first (n = 152) • No clopidogrel therapy (n = 140) • Some patients also randomized to receive a therapeutic or prophylactic dose of anticoagulation (n = 290) **Primary Endpoint** • Composite of VTE or ATEs by hospital discharge or Day 28. Events included death due to VTE or ATEs, PE, clinically evident DVT, MI, ischemic stroke, systemic embolic events or acute limb ischemia, and clinically silent DVT. **Secondary Endpoint** • Composite of clinically evident VTE or ATEs by hospital discharge or Day 28 **Safety Endpoints** • Fatal or life-threatening bleeding • Moderate or severe bleeding	**Participant Characteristics** • Median age 58 years; 41% women; 71% White • At baseline, 99% required HFNC, NIV, or MV; 15% required MV (37% required MV during the study) **Primary Outcome** • Composite of VTE or ATEs by hospital discharge or Day 28: 10% in both arms (win ratio 1.04; 95% CI, 0.54–2.01; P = 0.90) **Secondary Outcome** • Composite of clinically evident VTE or ATEs by hospital discharge or Day 28: 7% in clopidogrel arm vs. 9% in no clopidogrel arm (win ratio 0.79; 95% CI, 0.38–1.65; *P* = 0.53) **Safety Outcomes** • Fatal or life-threatening bleeding: 1.3% in clopidogrel arm vs. 1.4% in no clopidogrel arm (*P* = 1.00) • Moderate or severe bleeding: 4.0% in clopidogrel arm vs. 6.4% in no clopidogrel arm (*P* = 0.83)	**Key Limitations** • Open-label study (adjudication committee members were blinded to the study arms) • Stopped early because decreasing number of ICU admissions for patients with COVID-19 made recruitment difficult • 31% discontinued clopidogrel **Interpretation** • In patients with COVID-19 who required ICU-level care, clopidogrel did not reduce the incidence of thrombotic complications.

Key: ATE = arterial thrombotic event; BMI = body mass index; CrCl = creatinine clearance; CVD = cardiovascular disease; DM = diabetes mellitus; DVT = deep vein thrombosis; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; HFNC = high-flow nasal cannula; HIT = heparin-induced thrombocytopenia; HTN = hypertension; ICU = intensive care unit; IL = interleukin; LMWH = low-molecular-weight heparin; MI = myocardial infarction; MV = mechanical ventilation; NIV = noninvasive ventilation; NSAID = nonsteroidal anti-inflammatory drug; the Panel = the COVID-19 Treatment Guidelines Panel; PE = pulmonary embolism; RCT = randomized controlled trial; RDV = remdesivir; SOC = standard of care; ULN = upper limit of normal; VTE = venous thromboembolism

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Miscellaneous Drugs

Last Updated: December 1, 2022

Summary Recommendations
Colchicine • The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of **colchicine** for the treatment of nonhospitalized patients with COVID-19, except in a clinical trial **(BIIa)**. • The Panel **recommends against** the use of **colchicine** for the treatment of hospitalized patients with COVID-19 **(AI)**. **Fluvoxamine** • There is insufficient evidence for the Panel to recommend either for or against the use of fluvoxamine for the treatment of COVID-19. **Ivermectin** • The Panel **recommends against** the use of **ivermectin** for the treatment of COVID-19, except in clinical trials **(AIIa)**. **Intravenous Immunoglobulin** • The Panel **recommends against** the use of **intravenous immunoglobulin** (IVIG) for the treatment of acute COVID-19 in adults and children, 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. • The Panel recommends using **IVIG** in combination with low to moderate dose glucocorticoids in hospitalized patients for the treatment of multisystem inflammatory syndrome in children (MIS-C) **(AIIb)**. • The Panel **recommends against** the routine use of **IVIG monotherapy** for the treatment of MIS-C unless glucocorticoid use is contraindicated **(AIIb)**. **Metformin** • The Panel **recommends against** the use of **metformin** for the treatment of COVID-19 in nonhospitalized patients **(BIIa)** and hospitalized patients **(BIII)**, except in a clinical trial. • Patients with COVID-19 who are receiving **metformin** for an underlying condition should continue this therapy as directed by their health care provider **(AIII)**.
Each recommendation in the Guidelines receives 2 ratings that reflect the strength of the recommendation and the quality of the evidence that supports it. See Guidelines Development for more information.

Colchicine

Last Updated: May 31, 2022

Colchicine is an anti-inflammatory drug that is used to treat a variety of conditions, including gout, recurrent pericarditis, and familial Mediterranean fever.[1] Recently, the drug has been shown to potentially reduce the risk of cardiovascular events in those with coronary artery disease.[2] Colchicine has several potential mechanisms of action, including reducing the chemotaxis of neutrophils, inhibiting inflammasome signaling, and decreasing the production of cytokines, such as interleukin-1 beta.[3] When colchicine is administered early in the course of COVID-19, these mechanisms could potentially mitigate or prevent inflammation-associated manifestations of the disease. These anti-inflammatory properties coupled with the drug's limited immunosuppressive potential, favorable safety profile, and widespread availability have prompted investigation of colchicine for the treatment of COVID-19.

Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of **colchicine** for the treatment of nonhospitalized patients with COVID-19, except in a clinical trial **(BIIa)**.
- The Panel **recommends against** the use of **colchicine** for the treatment of hospitalized patients with COVID-19 **(AI)**.

Rationale: Nonhospitalized Patients

COLCORONA, a large, placebo-controlled, randomized trial that evaluated colchicine in outpatients with COVID-19, did not reach its primary efficacy endpoint of reducing hospitalizations and death.[4] However, in the subset of patients whose diagnosis was confirmed by a positive SARS-CoV-2 polymerase chain reaction (PCR) result from a nasopharyngeal swab, a slight reduction in hospitalizations was observed among those who received colchicine.

PRINCIPLE, an open-label, adaptive-platform, randomized trial that evaluated colchicine versus usual care, was stopped for futility when no significant difference was found between the colchicine and usual care recipients for the outcome of time to first self-reported recovery from COVID-19.[5]

The PRINCIPLE trial showed no benefit for colchicine, and the larger COLCORONA trial failed to reach its primary endpoint, found only a very modest effect of colchicine in the subgroup of patients with positive SARS-CoV-2 PCR results, and reported more gastrointestinal adverse events for those receiving colchicine. Therefore, the Panel **recommends against** the use of **colchicine** for the treatment of COVID-19 in nonhospitalized patients, except in a clinical trial **(BIIa)**.

Rationale: Hospitalized Patients

In the RECOVERY trial, a large, randomized trial in hospitalized patients with COVID-19, colchicine demonstrated no benefit with regard to 28-day mortality or any secondary outcomes.[6] Based on the results from this large trial, the Panel **recommends against** the use of **colchicine** for the treatment of COVID-19 in hospitalized patients **(AI)**.

Clinical Data for COVID-19

COLCORONA Trial: Nonhospitalized Patients

The COLCORONA trial was a double-blind, placebo-controlled, randomized trial in outpatients who

received a diagnosis of COVID-19 within 24 hours of enrollment.[4] Participants were aged ≥70 years or aged ≥40 years with at least 1 of the following criteria: body mass index ≥30, diabetes mellitus, uncontrolled hypertension, known respiratory disease, heart failure or coronary disease, fever ≥38.4°C within the past 48 hours, dyspnea at presentation, bicytopenia, pancytopenia, or the combination of high neutrophil count and low lymphocyte count. Participants were randomized 1:1 to receive placebo or colchicine 0.5 mg twice daily for 3 days, then once daily for 27 days. The primary endpoint was a composite of death or hospitalization by Day 30; secondary endpoints included components of the primary endpoint, as well as the need for mechanical ventilation by Day 30. Participants reported by telephone the occurrence of any study endpoints at 15 and 30 days after randomization; in some cases, clinical data were confirmed or obtained by medical chart reviews.

Results

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

Limitations

- The trial stopped at approximately 75% of the target enrollment, which may have limited the study's power to detect differences for the primary outcome.
- Some patient-reported clinical outcomes potentially were misclassified.

PRINCIPLE Trial: Nonhospitalized Patients

PRINCIPLE was a randomized, open-label, platform trial that evaluated colchicine in symptomatic, nonhospitalized patients with COVID-19.[5] Included participants had symptoms for ≤14 days and were aged ≥65 years or aged ≥18 years with comorbidities or shortness of breath. Participants were randomized to receive colchicine 0.5 mg daily for 14 days or usual care. The coprimary endpoints, which included time to first self-reported recovery or hospitalization or death due to COVID-19 by Day 28, were analyzed using a Bayesian model. Participants were followed through symptom diaries. Futility was defined as not reaching a clinically meaningful benefit (i.e., a hazard ratio ≥1.2, corresponding to about 1.5 days of faster recovery in the colchicine arm) for the endpoint of time to first self-reported recovery.

Results

- The study enrolled 4,997 participants: 212 participants were randomized to receive colchicine; 2,081 to receive usual care alone; and 2,704 to receive other treatments.
- The prespecified primary analysis included participants with a positive test for SARS-CoV-2 (156 participants in the colchicine arm; 1,145 in the usual care arm; and 1,454 in the other treatments

arm).

- The trial stopped early because of futility; the median time to self-reported recovery was similar in the colchicine arm and the usual care arm (HR 0.92; 95% CrI, 0.72–1.16).
- Analyses showed no significant differences between the colchicine and usual care arms for self-reported time to recovery and for hospitalizations or death due to COVID-19.
- There were no statistically significant differences between the colchicine and usual care arms for the secondary outcomes in both the primary analysis population and in the subgroups, including the subgroups based on symptom duration, baseline disease severity, age, and comorbidities.
- The occurrence of adverse events was similar in the colchicine and usual care arms.

Limitations

- The study had an open-label design.
- The sample size of the colchicine arm was small.

RECOVERY Trial: Hospitalized Patients

In the RECOVERY trial, hospitalized patients with COVID-19 were randomized 1:1 to receive colchicine (1 mg followed by 0.5 mg 12 hours later, then 0.5 mg twice daily for 10 days or until discharge) or usual care.[6]

Results

- The study enrolled 11,340 participants.
- At randomization, 94% of participants were receiving corticosteroids.
- In both arms, the primary endpoint of all-cause mortality at Day 28 occurred in 21% of participants (rate ratio 1.01; 95% CI, 0.93–1.10; $P = 0.77$).
- There were no statistically significant differences between the arms for the endpoints of median time to discharge alive, discharge from the hospital within 28 days, and receipt of mechanical ventilation or death.
- The incidence of new cardiac arrhythmias, bleeding events, and thrombotic events was similar in the 2 arms. Two serious adverse events were attributed to colchicine: 1 case of severe acute kidney injury and 1 case of rhabdomyolysis.

Limitation

- The study had an open-label design.

COLCOVID Trial: Hospitalized Patients

COLCOVID was a multicenter, open-label, randomized trial in hospitalized adults with confirmed or suspected SARS-CoV-2.[7] Patients were assigned 1:1 to receive either colchicine (1.5 mg followed by 0.5 mg orally within 2 hours of initial dose, then twice daily for 14 days or until hospital discharge) plus usual care or usual care alone.

Results

- The study enrolled 1,279 participants.
- There were no statistically significant differences between the colchicine and usual care arms for either of the coprimary outcomes, which were mortality by Day 28 (HR 0.88; 95% CI, 0.70–1.12) and mechanical ventilation or mortality by Day 28 (HR 0.83; 95% CI, 0.67–1.02).
- More individuals in the colchicine arm than in the usual care arm experienced diarrhea (11.3% vs.

4.5%).

Limitation

- The study had an open-label design.

GRECCO-19 Trial: Hospitalized Patients

GRECCO-19 was a prospective, open-label, randomized clinical trial that included patients with COVID-19 from 16 hospitals in Greece.[8] Participants were assigned 1:1 to receive colchicine (1.5 mg followed by 0.5 mg after 60 minutes, then 0.5 mg twice daily for up to 3 weeks or until hospital discharge, whichever comes first) plus the standard of care or the standard of care alone.

Results

- The study enrolled 105 participants.
- Fewer participants in the colchicine arm (1 of 55 participants) than in the standard of care arm (7 of 50 participants) reached the primary clinical endpoint of clinical status deterioration from baseline by 2 points on a 7-point clinical status scale (OR 0.11; 95% CI, 0.01–0.96).
- Participants in the colchicine arm were significantly more likely to experience diarrhea than those in the standard of care arm (45.5% vs. 18.0%; $P = 0.003$).

Limitations

- The study had an open-label design.
- The sample size and number of clinical events were small.

The results of several small, randomized trials and retrospective cohort studies that evaluated various doses and durations of colchicine in hospitalized patients with COVID-19 have been published in peer-reviewed journals or been made available as preliminary, non-peer-reviewed reports.[9-12] Some of those studies showed benefits of colchicine use, including less need for supplemental oxygen, improvements in clinical status on an ordinal clinical scale, and reductions in certain inflammatory markers. In addition, some studies reported higher discharge rates or fewer deaths among patients who received colchicine than among those who received comparator drugs or placebos. However, the findings from these studies are difficult to interpret due to significant design or methodological limitations, including small sample sizes, open-label designs, differences in the clinical and demographic characteristics of participants, and differences in the cotreatments (e.g., remdesivir, corticosteroids) permitted in the treatment arms.

Adverse Effects, Monitoring, and Drug-Drug Interactions

Common adverse effects of colchicine include diarrhea, nausea, vomiting, abdominal cramping and pain, bloating, and loss of appetite. In rare cases, colchicine is associated with serious adverse events, such as neuromyotoxicity and blood dyscrasias. Colchicine clearance is decreased in patients with impaired renal function and may require dose reduction along with increased monitoring for adverse effects. Significant increases in colchicine plasma levels may occur when colchicine is coadministered with drugs that inhibit cytochrome P450 (CYP) 3A4 or P-glycoprotein (P-gp), increasing the risk of colchicine-induced adverse effects. The risk of myopathy may be increased with concomitant use of certain HMG-CoA reductase inhibitors (e.g., atorvastatin, lovastatin, simvastatin) due to potential competitive interactions mediated by CYP3A4 and P-gp pathways.[13,14] Fatal colchicine toxicity has been reported in individuals with renal or hepatic impairment who received colchicine in conjunction with P-gp inhibitors or strong CYP3A4 inhibitors.

Considerations in Pregnancy

There are limited data on the use of colchicine in pregnancy. Fetal risk cannot be ruled out based on data from animal studies and the drug's mechanism of action. Colchicine crosses the placenta and has antimitotic properties, which raises a theoretical concern for teratogenicity. However, a recent meta-analysis did not find that colchicine exposure during pregnancy increased the rates of miscarriage or major fetal malformations. There are no data for colchicine use in pregnant women with acute COVID-19. Risks of use should be balanced against potential benefits.[13,15]

Considerations in Children

Colchicine is most commonly used in children to treat periodic fever syndromes and autoinflammatory conditions. Although colchicine is generally considered safe and well-tolerated in children, there are no data on the use of the drug to treat pediatric acute COVID-19 or multisystem inflammatory syndrome in children (MIS-C).

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Fluvoxamine

Last Updated: December 16, 2021

Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) that is approved by the Food and Drug Administration (FDA) for the treatment of obsessive-compulsive disorder and is used for other conditions, including depression. Fluvoxamine is not FDA-approved for the treatment of any infection.

Anti-Inflammatory Effect of Fluvoxamine and Rationale for Use in COVID-19

In a murine sepsis model, fluvoxamine was found to bind to the sigma-1 receptor on immune cells, resulting in reduced production of inflammatory cytokines.[1] In an in vitro study of human endothelial cells and macrophages, fluvoxamine reduced the expression of inflammatory genes.[2] Ongoing studies are establishing whether the anti-inflammatory effects of fluvoxamine observed in nonclinical studies also occur in humans and are clinically relevant in the setting of COVID-19.

Recommendation

- There is insufficient evidence for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of fluvoxamine for the treatment of COVID-19.

Rationale

Three randomized trials have studied the use of fluvoxamine for the treatment of nonhospitalized patients with COVID-19. In STOP COVID, a contactless, double-blind randomized placebo-controlled trial conducted in the United States among nonhospitalized adults with mild COVID-19 diagnosed within 7 days of symptom onset, fluvoxamine (100 mg up to 3 times daily for 15 days) reduced clinical deterioration at Day 15.[3] Clinical deterioration was defined as shortness of breath plus oxygen saturation (SpO_2) <92% or hospitalization plus SpO_2 <92%. This was a small study (≤80 participants per arm) with limited cases of clinical deterioration and a short follow-up period. In addition, 24% of participants stopped responding to surveys prior to Day 15.

The subsequent STOP COVID 2, a Phase 3 randomized controlled trial (ClinicalTrials.gov Identifier NCT04668950) that enrolled >700 participants in the United States and Canada, was stopped for futility by a data and safety monitoring board after lower than expected case rates and treatment effect were observed.[4]

TOGETHER is an adaptive platform, double-blind randomized placebo-controlled trial conducted in Brazil.[5] Nonhospitalized adults with COVID-19 and a known risk factor for progression to severe disease were randomized to fluvoxamine 100 mg twice daily (n = 741) or placebo (n = 756) for 10 days. Fluvoxamine use was associated with a lower risk of the primary composite outcome of retention in the emergency department for >6 hours or admission to a tertiary hospital (79 of 741 participants [11%] in the fluvoxamine arm vs. 119 of 756 participants [16%] in the placebo arm [relative risk 0.68; 95% CrI, 0.52–0.88]). Of note, 87% of the primary outcome events were hospitalizations. There was no statistically significant difference between study arms for the secondary outcomes of need for hospitalization or time to symptom resolution. There was no significant difference in mortality between study arms in the intention-to-treat (ITT) population (17 of 741 participants [2%] in the fluvoxamine arm vs. 25 of 756 participants [3%] in the placebo arm [OR 0.69; 95% CI, 0.36–1.27]). In a secondary, per-protocol analysis of participants who received >80% of possible doses, death was the outcome for 1 of 548 participants (<1%) in the fluvoxamine arm versus 12 of 618 participants (2%) in the placebo

arm (OR 0.09; 95% CI, 0.01–0.47). Participants in the fluvoxamine arm were less likely to present to an emergency setting for COVID-19 for any duration, although this analysis was not prespecified. Compared with those in the placebo arm, participants who received fluvoxamine were less adherent to therapy and discontinued therapy due to intolerance more often.

While fluvoxamine treatment significantly reduced the primary composite outcome in the TOGETHER trial (i.e., retention in the emergency department for >6 hours or admission to a tertiary hospital), the difference in hospitalizations between arms was not significant.[5] Defining the clinical relevance of the >6 hour emergency department observation time endpoint is difficult, especially its applicability to practice settings in different countries. Moreover, the endpoint has not been used in other studies of interventions for nonhospitalized patients at high risk for hospitalization and death. While a per-protocol analysis found a significant treatment effect for mortality in patients taking >80% of possible doses (assessed by patient self-report), no such benefit was found in the primary ITT analysis. The 80% threshold has no clear justification, and only 74% of participants in the fluvoxamine arm reached this level of adherence. Since per-protocol analyses are not randomized comparisons, they can introduce bias when adherence is associated with factors that influence the outcome; this bias cannot be excluded in this study. Notably, mortality in the placebo arm was substantially higher in those with ≤80% adherence than in those with >80% adherence, suggesting that factors other than adherence differed in the per-protocol population. Finally, including only participants who could tolerate fluvoxamine does not reflect the actual effectiveness of the drug, since intolerance and adherence appeared to be related.

Additional studies are needed to provide more specific, evidence-based guidance on the role of fluvoxamine for the treatment of COVID-19. Further details of the studies discussed are provided in Table 7a.

Adverse Effects, Monitoring, and Drug-Drug Interactions

When fluvoxamine is used to treat psychiatric conditions, the most common adverse effect is nausea, but adverse effects can include other gastrointestinal effects (e.g., diarrhea, indigestion), neurologic effects (e.g., asthenia, insomnia, somnolence, anxiety, headache), and rarely suicidal ideation.

Fluvoxamine is a cytochrome P450 (CYP) 2D6 substrate and a potent inhibitor of CYP1A2 and CYP2C19 and a moderate inhibitor of CYP2C9, CYP2D6, and CYP3A4.[6] Fluvoxamine can enhance the serotonergic effects of other SSRIs or monoamine oxidase inhibitors (MAOIs), resulting in serotonin syndrome; therefore, it should not be used within 2 weeks of receipt of other SSRIs or MAOIs. Fluvoxamine may enhance the anticoagulant effects of antiplatelets and anticoagulants; therefore, patients receiving these drugs should be closely monitored.

Considerations in Pregnancy

Fluvoxamine is not thought to increase the risk of congenital abnormalities; however, the data on its use in pregnancy are limited.[7,8] The association of SSRI use in the late third trimester with a small, increased risk of primary persistent pulmonary hypertension in newborns has not been excluded, although the absolute risk is likely low.[9] The risk of fluvoxamine use in pregnancy for the treatment of COVID-19 should be balanced with the potential benefit.

Considerations in Children

Fluvoxamine is approved by the FDA for the treatment of obsessive-compulsive disorder in children aged ≥8 years.[10] Adverse effects due to SSRI use seen in children are similar to those seen in adults, although children and adolescents appear to have higher rates of behavioral activation and vomiting than adults.[11] There are no data on the use of fluvoxamine for the prevention or treatment of COVID-19 in

children.

Clinical Trials

See ClinicalTrials.gov for the latest information on studies of fluvoxamine and COVID-19.

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Table 7a. Fluvoxamine: Selected Clinical Data

Last Updated: December 16, 2021

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

Methods	Results	Limitations and Interpretation
TOGETHER: Double-Blind, Adaptive RCT of Fluvoxamine in Nonhospitalized Patients With COVID-19 in Brazil[1]		
Key Inclusion Criteria • Aged ≥50 years or aged ≥18 years with comorbidities • Laboratory-confirmed SARS-CoV-2 infection • ≤7 days of symptoms **Key Exclusion Criteria** • Use of an SSRI • Severe mental illness • Cirrhosis, recent seizures, severe ventricular cardia arrythmia **Interventions** • Fluvoxamine 100 mg PO twice daily for 10 days (n = 741) • Placebo (route, dosing frequency, and duration for some patients may have differed from fluvoxamine) (n = 756) **Primary Endpoint** • Composite endpoint of emergency setting observation for >6 hours or hospitalization due to progression of COVID-19 within 28 days after randomization **Key Secondary Endpoints** • Occurrence of COVID-19-related hospitalizations • Time to symptom resolution	**Participant Characteristics** • Median age 50 years; 58% women; 95% self-identified as mixed race • 13% with uncontrolled HTN; 13% with type 2 DM; 50% with BMI ≥30 kg/m^2 • Mean of 3.8 days from symptom onset to randomization **Primary Outcome** • Proportion of patients who met the primary composite endpoint: 11% in fluvoxamine arm vs. 16% in placebo arm (relative risk 0.68; 95% CrI, 0.52–0.88) **Secondary Outcomes** • 87% of clinical events were hospitalizations. • No difference between arms in COVID-19-related hospitalizations: 10% in fluvoxamine arm vs. 13% in placebo arm (OR 0.77; 95% CI, 0.55–1.05) • No difference between arms in time to symptom resolution. • Adherence: 74% in fluvoxamine arm vs. 82% in placebo arm (OR 0.62; 95% CI, 0.48–0.81). 11% in fluvoxamine arm vs. 8% in placebo arm stopped drug due to issues of tolerability.	**Key Limitations** • The >6-hour emergency setting observation endpoint has not been used in other studies of interventions for nonhospitalized patients who are at high risk for hospitalization and death • As this was an adaptive platform trial where multiple investigational treatments or placebos were being evaluated simultaneously, not all patients in the placebo arm received a placebo that was matched to fluvoxamine by route of administration, dosing frequency, or duration of therapy • PP analyses are not randomized comparisons, and they introduce bias when adherence is associated with factors that influence the outcome • Adherence was self-reported and not verified **Interpretation** • Fluvoxamine reduced the proportion of patients who met the composite endpoint of COVID-19-related hospitalization or retention in an emergency setting for >6 hours.

Methods	Results	Limitations and Interpretation
TOGETHER: Double-Blind, Adaptive RCT of Fluvoxamine in Nonhospitalized Patients With COVID-19 in Brazil[1], continued		
• Proportion of patients who were adherent to study drugs, defined as receiving >80% of possible doses • Mortality in both the primary ITT population and a PP population that included patients who took >80% of the study medication doses	• Mortality (ITT): 2% in fluvoxamine arm vs. 3% in placebo arm (OR 0.68; 95% CI, 0.36–1.27) • Mortality (PP): <1% in fluvoxamine arm vs. 2% in placebo arm (OR 0.09; 95% CI, 0.01–0.47)	• The use of fluvoxamine did not impact the incidence of COVID-19-related hospitalizations. • It is difficult to define the clinical relevance of the >6-hour emergency setting observation endpoint and apply it to practice settings in different countries. • Fluvoxamine did not have a consistent impact on mortality. • Fluvoxamine did not impact time to symptom resolution.
STOP COVID: Double-Blind RCT of Fluvoxamine in Nonhospitalized Patients With COVID-19 in the United States[2]		

Key Inclusion Criteria
• Aged ≥18 years
• Positive SARS-CoV-2 PCR result
• ≤7 days of symptoms
Key Exclusion Criteria
• Immunocompromised
• Unstable medical comorbidities
Interventions
• Fluvoxamine 50 mg PO for 1 dose, then fluvoxamine 100 mg twice daily, then fluvoxamine 100 mg 3 times daily through Day 15 (n = 80)
• Placebo (n = 72)
Primary Endpoint
• Clinical deterioration within 15 days of randomization. Clinical deterioration was defined as:
  • Having dyspnea or being hospitalized for dyspnea or pneumonia; *and*
  • Having SpO_2 <92% on room air or requiring supplemental oxygen to attain SpO_2 ≥92%
Key Secondary Endpoint
• Hospitalization
	Participant Characteristics
	• Mean age 46 years; 72% women; 25% Black
	• 56% with obesity; 20% with HTN; 17% with asthma
	• Median of 4 days from symptom onset to randomization
	Primary Outcome
	• Clinical deterioration: 0% in fluvoxamine arm vs. 8.3% in placebo arm (absolute difference 8.7%; 95% CI, 1.8% to 16.4%)
	Secondary Outcome
	• No patients in fluvoxamine arm and 4 patients in placebo arm were hospitalized.
		Key Limitations
		• Small sample size
		• Short follow-up period
		• Ascertaining clinical deterioration was challenging because all assessments were done remotely
		• 24% of patients stopped responding to follow-up prior to Day 15 but were included in the final analysis
		Interpretation
		• Fluvoxamine reduced the proportion of patients who experienced clinical deterioration.
		• Due to significant limitations, it is difficult to draw definitive conclusions about the efficacy of using fluvoxamine to treat COVID-19.

Key: BMI = body mass index; DM = diabetes; HTN = hypertension; ITT = intention-to-treat; the Panel = the COVID-19 Treatment Guidelines Panel; PCR = polymerase chain reaction; PO = oral; PP = per protocol; RCT = randomized controlled trial; SpO_2 = oxygen saturation; SSRI = selective serotonin reuptake inhibitor

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Intravenous Immunoglobulin

Last Updated: December 1, 2022

Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of **intravenous immunoglobulin (IVIG)** for the treatment of acute COVID-19 in adults and children, 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.
- The Panel recommends using **IVIG** in combination with low to moderate dose glucocorticoids in hospitalized patients for the treatment of multisystem inflammatory syndrome in children (MIS-C) **(AIIb)**.
- The Panel **recommends against** the routine use of **IVIG monotherapy** for the treatment of MIS-C unless glucocorticoid use is contraindicated **(AIIb)**.

Rationale

It is unknown whether IVIG products derived from pooled donor plasma contain high titers of SARS-CoV-2 neutralizing antibodies. In addition, different lots of IVIG may have different titers of antibodies. Information on antibody titer is not reported in clinical trials that have evaluated IVIG and likely varies based on the dominant circulating variants and when the plasma products were collected. Although IVIG preparations may have general immunomodulatory effects, these theoretical effects do not appear to benefit patients with COVID-19.[1]

IVIG with or without corticosteroids has been used for the treatment of MIS-C. See Therapeutic Management of Hospitalized Pediatric Patients With Multisystem Inflammatory Syndrome in Children (MIS-C) (With Discussion on Multisystem Inflammatory Syndrome in Adults [MIS-A]) for the Panel's recommendations.

Clinical Data for COVID-19

A meta-analysis of 6 randomized controlled trials of non-SARS-CoV-2-specific IVIG with 472 patients demonstrated no survival benefit from the use of IVIG in patients with COVID-19 when compared with controls.[1] All of the included trials were conducted in 2020, when the presence of SARS-CoV-2 antibodies in blood donors was likely uncommon. None of the studies measured the titers of anti-SARS-CoV-2 antibodies, so the extent that these preparations may have contained SARS-specific antibodies is unknown. Blood supplies collected since that time likely have a higher level of these antibodies, and the IVIG derived from those supplies could be expected to have a higher level of SARS-specific antibodies. Use of non-SARS-CoV-2-specific IVIG for the treatment of COVID-19 should be limited to clinical trials.

Concentrated antibody preparations derived from pooled plasma collected from individuals who have recovered from COVID-19 can be manufactured as SARS-CoV-2 hyperimmunoglobulin (hIVIG). Treatment with SARS-CoV-2 hIVIG did not alter patient outcome in a large randomized controlled trial of hospitalized patients, and it is currently not available for clinical use in the United States.[2]

Considerations in Pregnancy

IVIG is commonly used in pregnancy for other indications, such as alloimmune thrombocytopenia.[3] However, given the lack of clear evidence of IVIG efficacy for the treatment of acute COVID-19 in nonpregnant adults, the Panel **recommends against** the use of **IVIG** for the treatment of acute COVID-19 in pregnant individuals, 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.

Considerations in Children

No pediatric comparative studies have evaluated the use of IVIG in patients with acute COVID-19. IVIG is used in pediatric patients for other indications, such as in combination with glucocorticoids for the initial immunomodulatory treatment of MIS-C.[4-7] However, given the lack of clear evidence of IVIG efficacy for the treatment of acute COVID-19 in adults, the Panel **recommends against** the use of **IVIG** for the treatment of acute COVID-19 in children, except in a clinical trial **(AIII)**. This recommendation should not preclude the use of IVIG when otherwise indicated.

For the Panel's recommendations for children with MIS-C, see Therapeutic Management of Hospitalized Pediatric Patients With Multisystem Inflammatory Syndrome in Children (MIS-C) (With Discussion on Multisystem Inflammatory Syndrome in Adults [MIS-A]).

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Ivermectin

Last Updated: April 29, 2022

Ivermectin is a Food and Drug Administration (FDA)-approved antiparasitic drug used to treat several neglected tropical diseases, including onchocerciasis, helminthiases, and scabies.[1] For these indications, ivermectin has been widely used and is generally well-tolerated.[1,2] Ivermectin is not approved by the FDA for the treatment of any viral infection.

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

Reports from in vitro studies suggest that ivermectin acts by inhibiting host importin alpha/beta-1 nuclear transport proteins, which are part of a key intracellular transport process.[3,4] Viruses hijack the process and enhance infection by suppressing the host's antiviral response. In addition, ivermectin docking may interfere with SARS-CoV-2 spike protein attachment to the human cell membrane.[5] Some studies of ivermectin have also reported potential anti-inflammatory properties, which have been postulated to be beneficial in people with COVID-19.[6-8]

Ivermectin has been shown to inhibit replication of SARS-CoV-2 in cell cultures.[9] However, pharmacokinetic and pharmacodynamic studies suggest that achieving the plasma concentrations necessary for the antiviral efficacy detected in vitro would require administration of doses up to 100-fold higher than those approved for use in humans.[10,11] Although ivermectin appears to accumulate in lung tissue, predicted systemic plasma and lung tissue concentrations are much lower than 2 μM, the half-maximal inhibitory concentration (IC_{50}) observed in vitro for ivermectin against SARS-CoV-2.[12-15] Subcutaneous administration of ivermectin 400 μg/kg had no effect on SARS-CoV-2 viral loads in hamsters.[16] However, there was a reduction in olfactory deficit (measured using a food-finding test) and a reduction in the interleukin (IL)-6:IL-10 ratio in lung tissues.

The safety and efficacy of ivermectin for the prevention and treatment of COVID-19 have been evaluated in clinical trials and observational cohorts. Summaries of the studies that informed The COVID-19 Treatment Guidelines Panel's (the Panel) recommendation can be found in Table 7b. The Panel reviewed additional studies, but these studies are not summarized in Table 7b because they have study design limitations or results that make them less definitive and informative.

Recommendation

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

Rationale

The results of several randomized trials and retrospective cohort studies of ivermectin use in patients with COVID-19 have been published in peer-reviewed journals or have been made available as manuscripts ahead of peer review. Most of these studies, especially studies completed earlier in the pandemic, had incomplete information and significant methodological limitations, which made excluding common causes of bias difficult. Many of these studies have not been peer reviewed, and some have now been retracted.

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

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

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

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

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

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

See Table 7b for summaries of the key studies that informed the Panel's recommendation.

Monitoring, Adverse Effects, and Drug-Drug Interactions

- Adverse effects of ivermectin may include dizziness, pruritus, nausea, or diarrhea.[21]
- Neurological adverse effects have been reported with the use of ivermectin for the treatment of onchocerciasis and other parasitic diseases, but it is not clear whether these adverse effects were caused by ivermectin or the underlying conditions.[22]
- Ivermectin is a minor cytochrome P450 3A4 substrate and a p-glycoprotein substrate.
- Ivermectin is generally given with water on an empty stomach; however, administering ivermectin with food increases its bioavailability.
- The FDA first issued a warning in April 2020 that ivermectin intended for use in animals **should not be used** to treat COVID-19 in humans. This warning was updated and reiterated in 2021.

Clinical Trials

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

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Table 7b. Ivermectin: Selected Clinical Data

Last Updated: April 29, 2022

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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Metformin

Last Updated: December 1, 2022

Metformin has been identified as a potential COVID-19 therapeutic agent because of its possible action against the proteins that are involved in translation, its antiviral activity in vitro, and its anti-inflammatory and antithrombotic activities.[1-4] Data from observational studies have suggested that patients who were receiving metformin as treatment for diabetes at the time of their COVID-19 diagnosis had a lower risk of progressing to severe COVID-19.[5-7] Randomized controlled trials have provided insight into the role of metformin in treating nonhospitalized patients with COVID-19. These trials are described below and in Table 7c.

Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of **metformin** for the treatment of COVID-19 in nonhospitalized patients **(BIIa)** and hospitalized patients **(BIII)**, except in a clinical trial.
- Patients with COVID-19 who are receiving **metformin** for an underlying condition should continue this therapy as directed by their health care provider **(AIII)**.

Rationale

Two randomized controlled trials (the TOGETHER and COVID-OUT trials) assessed the efficacy of metformin in nonhospitalized patients with COVID-19. Neither trial demonstrated a benefit of metformin in reducing the risk of hospitalization or death in patients with COVID-19. The Panel's recommendations are based on the results of these trials.

Other outpatient therapies (e.g., ritonavir-boosted nirmatrelvir [Paxlovid], remdesivir, molnupiravir) have been shown to be effective in preventing hospitalization or death in unvaccinated patients who are at high risk of disease progression.

Clinical Data

The TOGETHER trial was a placebo-controlled platform clinical trial that was conducted in Brazil.[8] The study enrolled nonhospitalized individuals who had symptomatic SARS-CoV-2 infection for ≤7 days, no history of COVID-19 vaccination, and an increased risk of progressing to severe disease. Patients were randomized to receive extended-release metformin 750 mg (n = 215) or placebo (n = 203) twice daily for 10 days.

The primary endpoint was a composite of retention in an emergency setting for >6 hours or hospitalization within 28 days of randomization. Secondary endpoints included viral clearance at Days 3 and 7, clinical improvement at Day 28, time to hospitalization or death, and the occurrence of adverse events. The study was stopped by the data and safety monitoring board for futility, as there was a low probability of demonstrating a difference between the study arms. Overall, there was no difference between the arms in the number of adverse events; however, the proportion of patients who experienced Grade 3 events was higher in the metformin arm (9.8%) than in the placebo arm (4.4%).

COVID-OUT was a Phase 3, double-blind, placebo-controlled 2 x 3 factorial trial that evaluated the effectiveness of metformin, ivermectin, and fluvoxamine in patients with COVID-19.[9] Patients were randomized to receive metformin or placebo in 1 factor, and ivermectin, fluvoxamine, or placebo in

the other factor. The study enrolled nonhospitalized adults within 3 days of a confirmed diagnosis of COVID-19 and ≤7 days from symptom onset. Patients were aged 30 to 85 years and overweight. Those with stage 4 or 5 chronic kidney disease or an estimated glomerular filtration rate (eGFR) of <45 mL/min/1.73 m^2 were excluded. The metformin arm included those assigned to receive immediate-release oral (PO) metformin (titrated over several days to a final daily dose of 1,500 mg) alone or in combination with ivermectin (390–470 µg/kg PO per day for 3 days) or fluvoxamine (50 mg PO twice daily for 14 days). The control arm included those who received placebo with or without ivermectin or fluvoxamine.

The primary endpoint was a composite of development of hypoxemia (defined as oxygen saturation ≤93%, as measured by a home pulse oximeter), emergency department (ED) visit, hospitalization, or death by Day 14. While this study was being conducted, the Food and Drug Administration (FDA) raised concerns about the accuracy of home pulse oximeters. Approximately 50% of the patients enrolled in this study had received a primary COVID-19 vaccine series. The analyses showed no benefit for any of the 3 investigational agents in preventing the primary endpoint. In addition, the use of these agents did not lower the severity of COVID-19 symptoms over 14 days. A prespecified secondary analysis determined that patients in the metformin arm had a lower risk of ED visit, hospitalization, or death than those in the control arm (adjusted OR 0.58; 95% CI, 0.35–0.94).

For more information on these trials, see Table 7c.

Monitoring, Adverse Effects, and Drug-Drug Interactions

The most common adverse effects of metformin are nausea, vomiting, diarrhea, and headache. Rarely, lactic acidosis may occur. The risk factors associated with lactic acidosis include older age, impaired renal or hepatic function, the use of iodinated contrast dye, cardiac dysfunction, metabolic disturbances, and excessive alcohol consumption. Metformin is not recommended for patients with an eGFR of <30 mL/min/1.73 m^2.

Metformin is a substrate of the human organic cation transporters OCT1 and OCT2. Drugs that inhibit these transporters may increase the systemic exposure of metformin and increase the risk of metformin-related adverse effects.

Considerations in Pregnancy

Metformin is commonly used in pregnant people. However, because clinical trials have not demonstrated a clinical benefit of metformin in nonpregnant adults with COVID-19, there is no justification for administering it to pregnant people to treat COVID-19 outside of a clinical trial.

Considerations in Children

Although metformin is approved by the FDA for the treatment of type 2 diabetes mellitus in children aged >10 years, clinical trials that have evaluated its use for the treatment of COVID-19 have not included people aged <18 years. Given the lack of evidence of efficacy in adults, the Panel **recommends against** the use of **metformin** for the treatment of COVID-19 in pediatric patients, except in a clinical trial **(AIII)**.

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Table 7c. Metformin: Selected Clinical Data

Last Updated: December 1, 2022

The Panel's recommendations for metformin are based on data from the clinical trials described in this table.

Methods	Results	Limitations and Interpretation
COVID-OUT: RCT of Metformin, Ivermectin, and Fluvoxamine in Nonhospitalized Adults With COVID-19 in the United States[1]		

Key Inclusion Criteria
• Aged 30–85 years
• BMI ≥25 (≥23 if Asian or Latinx)
• Laboratory-confirmed SARS-CoV-2 infection
• ≤7 days of COVID-19 symptoms
Key Exclusion Criteria
• Immunocompromised
• Hepatic impairment
• Stage 4–5 chronic kidney disease or eGFR <45 mL/min/1.73m^2
Interventions
• Immediate-release metformin 500 mg PO on Day 1, 500 mg twice daily on Days 2–5, and 500 mg in morning and 1,000 mg in evening on Days 6–14 (n = 663) in the following arms:
  • Metformin alone (n = 284)
  • Metformin plus IVM 390–470 µg/kg PO once daily for 3 days (n = 204)
  • Metformin plus fluvoxamine 50 mg PO twice daily for 14 days (n = 175)
• Control (n = 660), which included the following arms:
  • Placebo alone (n = 293)
  • IVM or fluvoxamine alone (n = 367)
	Participant Characteristics
	• Median age 46 years; 56% women; 82% White
	• Median BMI 30
	• 27% with CVD
	• 52% received primary COVID-19 vaccination series
	• Mean number of days of symptoms: 4.8 days
	• Approximately 66% enrolled during Delta-predominant period; approximately 23% enrolled during Omicron-predominant period
	Primary Outcomes
	• Proportion of patients who met the composite endpoint by Day 14: 154 (24%) in metformin arm vs. 179 (27%) in control arm (aOR 0.84; 95% CI, 0.66–1.09; *P* = 0.19)
	• No difference between those who received metformin alone vs. placebo alone in occurrence of primary endpoint (aOR 0.91; 95% CI, 0.62–1.33)
	• ED visit, hospitalization, or death by Day 14 in a prespecified secondary analysis: 27 (4.1%) in metformin arm vs. 48 (7.3%) in control arm (aOR 0.58; 95% CI, 0.35–0.94)
	• Hospitalization or death by Day 14 in a prespecified secondary analysis: 8 (1.2%) in metformin arm vs. 18 (2.7%) in control arm (aOR 0.47; 95% CI, 0.20–1.11)
		Key Limitations
		• Analyses of secondary endpoints were not adjusted for multiple comparisons.
		• Study included SpO_2 measurements using home pulse oximeters as 1 of the composite measures of the primary endpoint. However, the FDA has issued a statement concerning the accuracy of these home pulse oximeters, making this study endpoint less reliable.
		Interpretation
		• The use of metformin did not prevent the composite outcome of COVID-19–related hypoxemia, ED visit, hospitalization, or death.
		• Although the impact of metformin on the occurrence of ED visit, hospitalization, or death suggests a possible positive effect, these results cannot be considered definitive.

Methods	Results	Limitations and Interpretation
COVID-OUT: RCT of Metformin, Ivermectin, and Fluvoxamine in Nonhospitalized Adults With COVID-19 in the United States[1], continued		
Primary Endpoints • Composite of hypoxemia (SpO_2 ≤93%, as measured by a home pulse oximeter), ED visit, hospitalization, or death by Day 14 • A prespecified secondary analysis evaluated the risk of ED visit, hospitalization, or death by Day 14 **Key Secondary Endpoints** • Total symptom score by Day 14, as measured by a symptom severity scale • Drug discontinuation	**Secondary Outcomes** • No difference between arms in total symptom score by Day 14 • Drug discontinuation or interruption: 29% in metformin arm vs. 25% in placebo alone arm	
TOGETHER: RCT of Metformin in Nonhospitalized Patients With COVID-19 in Brazil[2]		

Key Inclusion Criteria
• Aged ≥50 years or aged ≥18 years with at least 1 comorbidity
• Positive rapid antigen test result for SARS-CoV-2 infection
• ≤7 days of COVID-19 symptoms
Key Exclusion Criteria
• Acute respiratory symptoms that required hospitalization
• Receipt of a COVID-19 vaccine
Interventions
• Extended-release metformin 750 mg PO twice daily for 10 days (n = 215)
• Placebo PO twice daily for 10 days (n = 203)
Primary Endpoint
• Composite of retention in ED for >6 hours or hospitalized for progression of COVID-19 by Day 28
	Participant Characteristics
	• Median age 52 years; 57% women; 91% self-identified as mixed race
	• 45% with BMI ≥30; 40% with HTN; 15% with DM
	• 44% had symptom onset within 0–3 days
	Primary Outcome
	• Study was stopped early by DSMB for futility. At the time the study was stopped, primary endpoint had occurred in 13% in metformin arm vs. 15% in placebo arm (relative risk 1.14; 95% CI, 0.73–1.81; probability of superiority 28%).
	Secondary Outcomes
	• No difference between arms in:
	  • Clinical improvement by Day 28 (OR 1.05; 95% CI, 0.71–1.56)
	  • Viral clearance by Day 7 (OR 0.99; 95% CI, 0.88–1.11)
	  • Time to hospitalization or death ($P = 0.53$)
	  • Occurrence of treatment-emergent AEs: Grade 3 AEs 9.8% in metformin arm vs. 4.4% in placebo arm (relative risk 2.11; 95% CI, 1.05–4.61)
		Key Limitations
		• The >6-hour ED retention endpoint has not been used in other studies of patients who are at high risk of hospitalization or death.
		• Study was stopped early for futility.
		• Vaccinated individuals were excluded from trial.
		Interpretation
		• This trial demonstrated no clinical benefit of metformin in nonhospitalized patients with COVID-19.
		• The use of metformin was associated with more grade 3 AEs than placebo.

Methods	Results	Limitations and Interpretation
TOGETHER: RCT of Metformin in Nonhospitalized Patients With COVID-19 in Brazil[2], continued		
Key Secondary Endpoints • Clinical improvement by Day 28 • Viral clearance by Day 7 • Time to hospitalization or death • Occurrence of AEs • Study adherence	• Did not complete all phases of the study: 22% in metformin arm vs. 12% in placebo arm	

Key: AE = adverse event; BMI = body mass index; CVD = cardiovascular disease; DM = diabetes mellitus; DSMB = data and safety monitoring board; ED = emergency department; eGFR= estimated glomerular filtration rate; FDA= Food and Drug Administration; HTN = hypertension; IVM = ivermectin; the Panel = the COVID-19 Treatment Guidelines Panel; PO = orally; RCT = randomized controlled trial; SpO_2 = oxygen saturation

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Table 7d. Characteristics of Miscellaneous Drugs

Last Updated: December 1, 2022

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

Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments
Colchicine *Not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*				
Dose for COVID-19 in COLCORONA Trial • Colchicine 0.5 mg twice daily for 3 days, then once daily for 27 days[1] **Dose for COVID-19 in COLCOVID Trial** • Colchicine 1.5 mg PO followed by 0.5 mg PO within 2 hours of initial dose, then 0.5 mg PO twice daily for 14 days or until hospital discharge, whichever comes first[2]	• Diarrhea • Nausea • Vomiting • Cramping • Abdominal pain • Bloating • Loss of appetite • Neuromyotoxicity (rare)[3] • Blood dyscrasias (rare)	• CBC • Renal function • Hepatic function	• P-gp and CYP3A4 substrate • The risk of myopathy may be increased with the concomitant use of certain HMG-CoA reductase inhibitors (e.g., atorvastatin, lovastatin, simvastatin) due to potential competitive interactions mediated by P-gp and CYP3A4 pathways. • Fatal colchicine toxicity has been reported in individuals with renal or hepatic impairment who used colchicine in conjunction with P-gp inhibitors or strong CYP3A4 inhibitors.	• Use of colchicine should be avoided in patients with severe renal insufficiency. Patients with moderate renal insufficiency who receive the drug should be monitored for AEs. **Availability** • In the COLCORONA and COLCOVID trials, 0.5 mg colchicine tablets were used for dosing; in the

Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments
Colchicine, continued				
				United States, colchicine is available as 0.6 mg tablets.
Fluvoxamine *Not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*				
Doses for COVID-19 in Clinical Trials • Fluvoxamine 50 mg twice daily • Fluvoxamine 100 mg twice daily • Fluvoxamine 100 mg 3 times daily	• Nausea • Diarrhea • Dyspepsia • Asthenia • Insomnia • Somnolence • Sweating • Suicidal ideation (rare)	• Hepatic function • Drug interactions • Withdrawal symptoms during dose tapering	• CYP2D6 substrate • Fluvoxamine inhibits several CYP isoenzymes (CYP1A2, CYP2C9, CYP3A4, CYP2C19, CYP2D6). • Coadministration of tizanidine, thioridazine, alosetron, or pimozide with fluvoxamine is **contraindicated**.	• Fluvoxamine may enhance anticoagulant effects of antiplatelets and anticoagulants; consider additional monitoring when these drugs are used concomitantly with fluvoxamine. • The use of MAOIs concomitantly with fluvoxamine or within 14 days of treatment with fluvoxamine is **contraindicated**.
Intravenous Immunoglobulin *Primarily used for the treatment of MIS-C. Currently under investigation in clinical trials.*				
Dose for MIS-C • IVIG 2 g/kg IBW/dose (up to a maximum total dose of 100 g) IV for 1 dose • In the event of cardiac dysfunction or fluid overload, consider dividing the dose (IVIG 1 g/kg IBW/dose IV every 24 hours for 2 doses).	• Allergic reactions, including anaphylaxis • Renal failure • Thrombotic events • Aseptic meningitis syndrome • Hemolysis • TRALI • Transmission of infectious pathogens • AEs may vary by formulation. • AEs may be increased with high dose or rapid infusion.	• Transfusion-related reactions • Vital signs at baseline and during and after infusion • Renal function; discontinue treatment if renal function deteriorates.	• Not a CYP substrate; no drug interaction expected	• Rapid infusion should be avoided in patients with renal dysfunction or who are at risk of thromboembolic events.

Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments
Ivermectin *Not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*				
Doses for COVID-19 in Clinical Trials • IVM 200–600 µg/kg PO as a single dose or a once-daily dose for up to 5 days	• Dizziness • Pruritus • GI effects (e.g., nausea, diarrhea) • Neurological AEs have been reported when IVM has been used to treat parasitic diseases, but it is not clear whether these AEs were caused by IVM or the underlying conditions.	• Monitor for potential AEs.	• Minor CYP3A4 substrate • P-gp substrate	• Generally given on an empty stomach with water; however, administering IVM with food increases its bioavailability.[4]
Metformin *Not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*				
Doses for COVID-19 in Clinical Trials • Metformin (immediate-release) 500 mg on Day 1, 500 mg twice daily on Days 2–5, and 500 mg in morning and 1,000 mg in evening on Days 6–14 • Metformin (extended release) 750 mg twice daily for 10 days	• Diarrhea • Nausea and vomiting • Headache • Lactic acidosis	• Renal function • Hepatic function • Drug interactions • Alcohol use disorder	• OCT1 and OCT2 substrate • Drugs that interfere with OCT systems (e.g., cimetidine, dolutegravir, ranolazine, vandetanib) could increase systemic exposure to metformin. • Concomitant use with carbonic anhydrase inhibitors (including acetazolamide, topiramate, and zonisamide) may increase the risk of lactic acidosis.	• Alcohol intake may increase the risk of lactic acidosis.

Key: AE = adverse event; CBC = complete blood count; CYP = cytochrome P450; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; GI = gastrointestinal; IBW = ideal body weight; IV = intravenous; IVIG = intravenous immunoglobulin; IVM = ivermectin; MAOI = monoamine oxidase inhibitor; MIS-C = multisystem inflammatory syndrome in children; OCT = organic cation transporter; the Panel = the COVID-19 Treatment Guidelines Panel; P-gp= P-glycoprotein; PO = orally; TRALI = transfusion-related acute lung injury

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Supplements

Last Updated: December 1, 2022

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 in nonhospitalized patients. • 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 hospitalized patients. **Vitamin D** • There is insufficient evidence for the Panel to recommend either for or against the use of vitamin D for the prevention or 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 (i.e., zinc 11 mg daily for men, zinc 8 mg daily for nonpregnant women) for the prevention of COVID-19, except in a clinical trial **(BIII)**.
Each recommendation in the Guidelines receives 2 ratings that reflect the strength of the recommendation and the quality of the evidence that supports it. See Guidelines Development for more information.

Vitamin C

Last Updated: September 26, 2022

Since the most recent revision of this section, the results from several cohort studies, clinical trials, and meta-analyses on the use of vitamin C in patients with COVID-19 have been published in peer-reviewed journals or have been made available as manuscripts before peer review. However, most of these studies had significant limitations, such as a small sample size or a lack of randomization or blinding. In addition, the study designs had different doses or formulations of vitamin C and different outcome measures, and the study populations included patients with varying concomitant medications and COVID-19 disease severity. The studies summarized in this section have had the greatest impact on the COVID-19 Treatment Guidelines Panel's (the Panel) recommendations. Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide further guidance on the role of vitamin C in the prevention and treatment of COVID-19.

Vitamin C (ascorbic acid) is a water-soluble vitamin that has been considered for potential beneficial effects in patients with varying degrees of illness severity. It is an antioxidant and free radical scavenger that has anti-inflammatory properties, influences cellular immunity and vascular integrity, serves as a cofactor in endogenous catecholamine generation, and has been studied in many disease states,[1,2] including COVID-19.

Recommendation for Nonhospitalized 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 nonhospitalized 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 for Nonhospitalized Patients With COVID-19

In an open-label trial conducted at 2 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 endpoint 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 $P = 0.45$). No serious adverse events were related to the treatments, although nonserious adverse events (primarily gastrointestinal) occurred more frequently in patients who received supplements than in those who did not. Zero percent of patients in the standard of care arm, 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 (overall $P < 0.001$).

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 2 supplements, when compared with standard care, did not significantly decrease the number of days required to reach a 50% reduction in a symptom severity score.

Recommendation for Hospitalized 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 hospitalized patients.

Rationale

No controlled trials have definitively demonstrated a clinical benefit of vitamin C in critically ill patients with COVID-19, and the available observational data are inconclusive. Studies of vitamin C regimens in patients with acute respiratory distress syndrome (ARDS) or sepsis not related to COVID-19 have reported variable efficacy and few safety concerns.

Clinical Data for Hospitalized Patients

Intravenous Vitamin C in Hospitalized Patients With COVID-19

In a small, prospective, open-label randomized trial of hospitalized patients with severe COVID-19 in Pakistan, patients were randomized to receive intravenous (IV) vitamin C 50 mg/kg per day plus standard therapy (n = 75) or standard therapy alone (n = 75).[4] Standard therapy included antipyretics, dexamethasone, and prophylactic antibiotics. Vitamin C recipients became symptom-free earlier (7.1 days vs. 9.6 days; $P < 0.0001$) and had a shorter duration of hospitalization (8.1 days vs. 10.7 days; $P < 0.0001$) than patients who received standard therapy alone. There were no significant differences between the arms for the outcomes of mortality and the need for mechanical ventilation. Limitations of this study include a small sample size, enrollment from only 1 hospital, and no clear method for recording symptoms.

In a pilot trial in China, 56 adults with COVID-19 who were in the intensive care unit (ICU) were randomized to receive vitamin C 24 g IV per day for 7 days or placebo. The study was terminated early due to a reduction of cases of COVID-19 in China.[5] Overall, the study found no differences between the arms for the outcomes of mortality, duration of mechanical ventilation, or 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; $P = 0.04$).

In a randomized trial of 66 hospitalized patients with COVID-19 who required supplemental oxygen, treatment with IV vitamin C at doses escalating from 0.3 g/kg to 0.9 g/kg over 6 days (n = 44) was compared to standard of care (n = 22).[6] IV vitamin C did not improve the primary outcome of clinical status (defined as a composite of a 50% reduction in oxygen use, a 50% reduction in bronchodilator use, or hospital discharge) at 72 hours after randomization.

Intravenous Vitamin C in Hospitalized Patients Without COVID-19

In critically ill patients with conditions similar to COVID-19, such as sepsis and ARDS, vitamin C has been studied alone and in combination with thiamine and corticosteroids. In a randomized trial of 862 patients with sepsis who were in the ICU and required vasopressors, treatment with vitamin C 200 mg/kg IV per day for 4 days was compared to treatment with placebo.[7] The vitamin C arm had more deaths (35.4% vs. 31.6%) and more cases of persistent organ dysfunction (9.1% vs. 6.9%) at 28 days. The results demonstrated a significant difference between the arms for the composite primary outcome of death or persistent organ dysfunction (44.5% vs. 38.5%; $P = 0.01$). For the subgroup of patients with

sepsis and COVID-19 (n = 63), there was no statistical difference between the arms for the composite primary outcome.

In a randomized trial among patients with sepsis-induced ARDS who were receiving mechanical ventilation (n = 167), patients who received vitamin C 200 mg/kg IV per day for 4 days or placebo had similar SOFA scores and levels of inflammatory markers.[8] However, 28-day mortality was lower in the vitamin C arm than in the placebo arm (29.8% vs. 46.3%; 95% CI, 2% to 31.1%; $P = 0.03$). The vitamin C arm also had more days alive, ICU-free days, and hospital-free days than the placebo arm.

Several randomized trials found no consistent clinical benefit in patients who received vitamin C and thiamine, with or without hydrocortisone, for the treatment of sepsis or septic shock. Two trials observed reductions in organ dysfunction (as measured by a change in SOFA score on Day 3)[9,10] or the duration of shock[11] with no effect on clinical outcomes. Three other trials, including a large trial of 501 patients with sepsis, found no differences between the treatment and placebo arms for any physiologic or outcome measures.[12-14] A meta-analysis found that in patients with sepsis not related to COVID-19, vitamin C therapy did not reduce mortality but may have improved organ dysfunction over 72 to 96 hours. However, this effect may have been mediated by thiamine and hydrocortisone rather than vitamin C.[15] These studies on vitamin C in patients without COVID-19 have conflicting results. Therefore, there is insufficient evidence to determine whether the use of vitamin C will benefit or harm patients with COVID-19.

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

Other Considerations

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: September 26, 2022

Since the last revision of this section, the results from several cohort studies, clinical trials, and meta-analyses on the use of vitamin D for the prevention or treatment of COVID-19 have been published in peer-reviewed journals or have been made available as manuscripts ahead of peer review. However, most of these studies had significant limitations, such as small sample sizes or a lack of randomization and/or blinding. In addition, these studies used varying doses and formulations of vitamin D, enrolled participants with a range of COVID-19 severities, included different concomitant medications, and measured different study outcomes. All these factors make it difficult to compare results across studies. The studies summarized below are those that have had the greatest impact on the COVID-19 Treatment Guidelines Panel's (the Panel) recommendations.

Although multiple observational cohort studies suggest that people with low vitamin D levels are at increased risk of SARS-CoV-2 infection and worse clinical outcomes after infection (e.g., higher mortality rates), clear evidence that vitamin D supplementation provides protection against infection or improves outcomes in patients with COVID-19 is still lacking.[1,2]

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.[3] It is postulated that these immunomodulatory effects of vitamin D could potentially protect against SARS-CoV-2 infection or decrease the severity of COVID-19.

Vitamin D deficiency (defined as a serum concentration of 25-hydroxyvitamin D ≤20 ng/mL) is common in the United States, particularly among persons of Hispanic ethnicity and Black race.[4] These groups are overrepresented among cases of COVID-19 in the United States.[5] 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.[6] High levels of vitamin D may cause hypercalcemia and nephrocalcinosis.[7]

Clinical Data on Vitamin D for Prevention

In a double-blind trial conducted at 4 hospitals in Mexico, frontline health care workers were randomized to receive vitamin D_3 4,000 IU or placebo for 30 days.[8] Participants were enrolled before COVID-19 vaccines became available. Over one-third of the enrolled participants dropped out before study completion. Of the 192 participants who completed follow-up, 6.4% of participants in the vitamin D_3 arm and 24.5% in the placebo arm acquired SARS-CoV-2 infection (relative risk 0.22; 95% CI, 0.08–0.59). At baseline, approximately 67% of participants had vitamin D deficiency, but this was not found to be an independent predictor of acquiring SARS-CoV-2 infection. The frequency of SARS-CoV-2 infection was very high in the placebo group, and it is unclear how these results translate to the use of vitamin D in vaccinated health care workers.

Clinical Data on Vitamin D for Treatment

In a double-blind trial conducted from June to October 2020 at 2 sites in Brazil, 240 hospitalized patients with moderate to severe COVID-19 were randomized to receive a single dose of vitamin D_3 200,000 IU or placebo.[9] Patients were considered to have moderate to severe COVID-19 if they had a positive polymerase chain reaction (PCR) result for SARS-CoV-2 or compatible computed tomography scan findings and a respiratory rate >24 breaths/min or oxygen saturation <93% on room air. The primary outcome was length of hospital stay. The study found no significant difference in the median length of stay 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; log-rank $P = 0.59$). No significant differences were observed between the arms in the proportion of patients who were admitted to the intensive care unit (ICU), the need for mechanical ventilation, or mortality. There were no significant safety concerns.

A randomized, double-blind, placebo-controlled study conducted in Argentina included 218 adult patients with COVID-19 who had been admitted to the hospital during the preceding 24 hours and who had oxygen saturation ≥90% on room air and a risk factor for disease progression.[10] Patients were randomized to receive a single oral dose of vitamin D_3 500,000 IU or placebo. The primary outcome was the change in the respiratory sepsis-related organ failure assessment (rSOFA) score between baseline and the highest value recorded up to Day 7. There was no significant difference between the arms for this outcome, with a median change of 0 in both arms ($P = 0.925$). There were also no significant differences between the arms in the median length of hospital stay, the number of patients admitted to the ICU, or in-hospital mortality.

A randomized, open-label study conducted in France compared the effect of a high dose of vitamin D_3 400,000 IU to the standard dose of vitamin D_3 50,000 IU on mortality in 254 patients who were either hospitalized or living in nursing facilities near the study hospital sites.[11] Patients were aged ≥65 years, had been diagnosed with SARS-CoV-2 infection within the preceding 3 days, and had at least 1 risk factor for disease progression (i.e., aged ≥75 years, hypoxemia). Mortality was significantly different between the arms at 14 days, with 7 deaths (6%) among patients in the high-dose arm and 14 deaths (11%) among patients in the standard-dose arm (adjusted HR 0.33; 95% CI, 0.12–0.86; $P = 0.02$). However, mortality was not significantly different between the arms at 28 days (adjusted HR 0.70; 95% CI, 0.36–1.36; $P = 0.29$).

In an open-label pilot study, 50 hospitalized adults in New York with PCR-confirmed SARS-CoV-2 infection were randomized to receive calcitriol 0.5 µg daily for 14 days or no treatment.[12] Calcitriol is the active metabolite of cholecalciferol or vitamin D_3 and is more commonly used to treat parathyroid disease. The study evaluated the change in the patients' oxygen saturation between admission and discharge. Additional outcomes were the length of hospital stay; mortality; and the need for endotracheal intubation, ICU admission, or hospital readmission within 30 days. Oxygen saturation was calculated using the ratio of peripheral arterial oxygen saturation (measured by pulse oximetry) to fraction of inspired oxygen (SpO_2/FiO_2) as a surrogate for the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2).

Between admission and discharge, the patients who received no treatment had an average increase of 13.2 (SD ±127.7) in the SaO_2/FiO_2 ratio and those who received calcitriol had an increase of 91.04 (SD ±119.08; $P = 0.0305$), implying an improvement in oxygenation.[12] There were no differences between the arms in the length of hospital stay, mortality, or the need for ICU admission or hospital readmission.

More information on the clinical trials that are evaluating the use of vitamin D can be found on ClinicalTrials.gov.

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Zinc

Last Updated: September 26, 2022

Since the last revision of this section, the results from some cohort studies and clinical trials on the use of zinc in patients with COVID-19 have been published in peer-reviewed journals or have been made available as manuscripts ahead of peer review. However, most of these studies had significant limitations, such as small sample sizes or a lack of randomization or blinding. In addition, these studies used varying doses and formulations of zinc, enrolled participants with a range of COVID-19 severities, included different concomitant medications, and measured different study outcomes. All these factors make it difficult to compare results across studies. In addition, several studies used zinc in combination with hydroxychloroquine, and the COVID-19 Treatment Guidelines Panel (the Panel) recommends against the use of hydroxychloroquine for the treatment of COVID-19 (see Antiviral Agents, Including Antibody Products).

The studies summarized below are those that have had the greatest impact on the Panel's recommendations. Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide further guidance on the role of zinc in the prevention and treatment of COVID-19.

Recommendations

- 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 (i.e., zinc 11 mg daily for men, zinc 8 mg daily for nonpregnant women) for the prevention of COVID-19, except in a clinical trial **(BIII)**.

Rationale

Increased intracellular zinc concentrations efficiently impair the replication of 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. Zinc levels are difficult to measure accurately, as zinc is distributed as a component of various proteins and nucleic acids.[3] See ClinicalTrials.gov for more information about ongoing studies. None of the results that are currently available from clinical trials provide evidence of a clinical benefit of zinc for the treatment or prevention of COVID-19.

The recommended dietary allowance for elemental zinc is 11 mg daily for men and 8 mg daily for nonpregnant women.[4] 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.

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).[5-7] The use of zinc supplementation for durations as short as 10 months has been associated with copper deficiency.[3] In addition, oral zinc can decrease the absorption of medications that bind with polyvalent cations.[4] 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

In an open-label trial that was conducted at 2 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.[8] The primary endpoint 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). Compared with standard of care, treatment with high-dose zinc gluconate, ascorbic acid, or a combination of the 2 supplements did not significantly decrease the number of days required to reach a 50% reduction in a symptom severity score. 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.

In a randomized clinical trial that was conducted at 3 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.[9] The primary endpoints were recovery within 28 days, the need for mechanical ventilation, and death. The 2 arms were matched for age and gender. There were no significant differences between the arms in the percentages of patients who recovered within 28 days (79.2% in the zinc plus hydroxychloroquine arm vs. 77.9% in the hydroxychloroquine alone 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.

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Considerations for Using Concomitant Medications in Patients With COVID-19

Last Updated: December 16, 2021

Summary Recommendations
• Patients with COVID-19 who are receiving concomitant medications (e.g., angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], HMG-CoA reductase inhibitors [statins], systemic or inhaled corticosteroids, nonsteroidal anti-inflammatory drugs, acid-suppressive therapy) for underlying medical conditions **should not discontinue** these medications during acute management of COVID-19 unless discontinuation is otherwise warranted by their clinical condition (**AIIa** for **ACE inhibitors and ARBs**; **AIII** for **other medications**). • The COVID-19 Treatment Guidelines Panel **recommends against** using medications off-label to treat COVID-19 if they have not been shown to be safe and effective for this indication in a clinical trial **(AIII)**.
Each recommendation in the Guidelines receives 2 ratings that reflect the strength of the recommendation and the quality of the evidence that supports it. See Guidelines Development for more information.

Individuals with underlying medical conditions, such as cardiovascular disease, pulmonary disease, diabetes, and malignancy, and those who receive chronic immunosuppressive therapy are at higher risk of severe illness with COVID-19. These patients are often prescribed medications to treat their underlying medical conditions.

Early in the pandemic, some of these medications, such as angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs),[1] HMG-CoA reductase inhibitors (statins),[2,3] and H-2 receptor antagonists,[4] were hypothesized to offer potential as COVID-19 therapeutic agents. Others, such as nonsteroidal anti-inflammatory agents (NSAIDs), were postulated to have negative impacts.[5] Currently, there is no evidence that discontinuing medication for underlying medical conditions offers a clinical benefit for patients with COVID-19.[6-8] For example, the Food and Drug Administration stated that there is no evidence linking the use of NSAIDs with worsening of COVID-19 and advised patients to use them as directed.[9] Additionally, the American Heart Association, the Heart Failure Society of America, and the American College of Cardiology issued a joint statement that renin-angiotensin-aldosterone system antagonists, such as ACE inhibitors and ARBs, should be continued as prescribed in those with COVID-19.[10]

Therefore, patients with COVID-19 who are treated with concomitant medications for an underlying medical condition **should not discontinue** these medications during acute management of COVID-19 unless discontinuation is otherwise warranted by their clinical condition **(AIII)**. For patients with COVID-19 who require nebulized medications, precautions should be taken to minimize the potential for transmission of SARS-CoV-2 in the home and in health care settings.[11,12]

The COVID-19 Treatment Guidelines Panel **recommends against** using medications off-label to treat COVID-19 if they have not been shown to be safe and effective for this indication in a clinical trial **(AIII)**. Clinicians should refer to the Therapies section of the Guidelines for information on the medications that have been studied as potential therapeutic options for patients with COVID-19.

When prescribing medications to treat COVID-19, clinicians should always assess the patient's current medications for potential drug-drug interactions and/or additive adverse effects.[13] The decision to continue or change a patient's medications should be individualized based on their specific clinical condition.

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Special Considerations in People Who Are Immunocompromised

Last Updated: December 1, 2022

Summary Recommendations

Prevention of COVID-19

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends COVID-19 vaccination for all people who are moderately or severely immunocompromised **(AIII)**.
- All close contacts of people who are immunocompromised are strongly encouraged to be up to date on vaccination against COVID-19 **(AIII)**. Vaccinating household members, close contacts, and health care workers who provide care for patients who are immunocompromised is important to protect these patients from infection.
- The Panel recommends using **tixagevimab plus cilgavimab (Evusheld)** as SARS-CoV-2 pre-exposure prophylaxis (PrEP) for adults and adolescents who do not have SARS-CoV-2 infection or recent exposure to an individual with SARS-CoV-2 infection and who are moderately to severely immunocompromised and may have an inadequate immune response to COVID-19 vaccination **(BIIb)**.
- There is insufficient evidence for the Panel to recommend either for or against the use of SARS-CoV-2 serologic testing to assess for immunity or to guide clinical decisions about using COVID-19 vaccines or anti-SARS-CoV-2 monoclonal antibodies (mAbs) for PrEP.

General Management of Patients With COVID-19 Who Are Immunocompromised

- The Panel recommends that decisions regarding stopping or reducing the doses of immunosuppressive drugs in patients with COVID-19 be made in consultation with the appropriate specialists; clinicians should consider factors such as the underlying disease, the specific immunosuppressants being used, the potential for drug-drug interactions, and the severity of COVID-19 **(BIII)**.

Therapeutic Management of Nonhospitalized Patients With COVID-19 Who Are Immunocompromised

- The Panel recommends prompt treatment with antivirals or anti-SARS-CoV-2 mAbs for nonhospitalized patients with mild to moderate COVID-19 who are immunocompromised **(AIII)**. Specific recommendations are outlined in the text.

Therapeutic Management of Hospitalized Patients With COVID-19 Who Are Immunocompromised

- For most patients with COVID-19 who are immunocompromised, the Panel recommends using antiviral drugs and immunomodulatory therapies at the doses and durations that are recommended for the general population **(AIII)**.
- In some cases, immunomodulatory drug regimens may need to be adjusted to reduce the risk of drug-drug interactions, overlapping toxicities, and secondary infections.
- There is insufficient evidence to guide clinical recommendations on using combination therapies (e.g., an antiviral drug plus an anti-SARS-CoV-2 mAb) or extending the duration of treatment beyond the duration authorized by the Food and Drug Administration.
- There is insufficient evidence for the Panel to recommend either for or against the use of high-titer COVID-19 convalescent plasma (CCP) for the treatment of COVID-19 in hospitalized or nonhospitalized patients who are immunocompromised.
  - Some Panel members would use CCP to treat an immunocompromised patient with significant symptoms attributable to COVID-19 and with signs of active SARS-CoV-2 replication and who is having an inadequate response to available therapies. In these cases, clinicians should attempt to obtain high-titer CCP from a vaccinated donor who recently recovered from COVID-19 likely caused by a SARS-CoV-2 variant similar to the variant causing the patient's illness.
- People who are immunocompromised and have COVID-19 but were hospitalized for conditions other than COVID-19 should receive the same treatments as nonhospitalized patients **(AIII)**.

Each recommendation in the Guidelines receives 2 ratings that reflect the strength of the recommendation and the quality of the evidence that supports it. See Guidelines Development for more information.

Approximately 3% of Americans have immunocompromising conditions.[1] People who are immunocompromised are a heterogeneous population, and the severity of COVID-19 can vary significantly in this group. Some individuals who are immunocompromised may have a higher risk of hospitalization, complications, or death, and some may have outcomes that are comparable to those in the general population.

This section pertains to people who are moderately or severely immunocompromised, which includes those who:

- Are receiving active treatment for solid tumor and hematologic malignancies.
- Have hematologic malignancies (e.g., chronic lymphocytic lymphoma, non-Hodgkin lymphoma, multiple myeloma, acute leukemia) and are known to have poor responses to COVID-19 vaccines or an increased risk of severe COVID-19, regardless of the treatment status for the hematologic malignancy.
- Received a solid-organ or islet transplant and are receiving immunosuppressive therapy.
- Received chimeric antigen receptor T cell (CAR T-cell) therapy or a hematopoietic cell transplant (HCT) and are within 2 years of transplantation or are receiving immunosuppressive therapy.
- Have a moderate or severe primary immunodeficiency (e.g., severe combined immunodeficiency, DiGeorge syndrome, Wiskott-Aldrich syndrome, common variable immunodeficiency disease).
- Have advanced or untreated HIV infection (defined as people with HIV and CD4 T lymphocyte [CD4] cell counts <200 cells/mm^3, a history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV).
- Are receiving active treatment with high-dose corticosteroids (i.e., ≥20 mg prednisone or equivalent per day when administered for ≥2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, or immunosuppressive or immunomodulatory biologic agents (e.g., B cell-depleting agents).

Data are evolving on the clinical outcomes of COVID-19 in people who are immunocompromised. Analyses have found a higher risk of hospitalization or death from COVID-19 in those with a variety of immunocompromising conditions, including rheumatic diseases, hematological malignancies, solid organ transplants, and HIV.[2-7] Factors that increase the risk of severe COVID-19 in the general population, such as older age, chronic kidney disease, cardiovascular disease, and other comorbidities, are significant drivers of risk in immunocompromised individuals. Moreover, some immunodeficiencies seem to increase the risk above and beyond traditional risk factors. For example, there is evidence that individuals who make autoantibodies to type I interferons, proteins critical to the protective immune response against viral infections, have a higher risk of severe COVID-19.[8] Similarly, certain classes of medications, such as T cell-depleting or T cell-suppressing agents (e.g., antithymocyte globulin, calcineurin inhibitors, mycophenolate mofetil, belatacept) or B cell-depleting agents (e.g., rituximab, ocrelizumab, obinutuzumab), have been associated with more severe COVID-19 outcomes.[9,10]

Prolonged shedding of SARS-CoV-2 has been reported in patients who are immunocompromised. A systematic review found that replication-competent virus could be detected for a median of 20 days in these patients, compared to 11 days in the general population.[11] Prolonged viral shedding may affect SARS-CoV-2 testing strategies and isolation durations for this group of patients. Moreover, case reports suggest that prolonged infections can create evolutionary pressure for the emergence of variants that resist therapies or evade vaccine-induced immunity.[12-14] There is currently insufficient evidence to guide clinical recommendations on using combinations of antiviral drugs and/or anti-SARS-CoV-2

monoclonal antibodies (mAbs) for the treatment of COVID-19. There are also no data to support extending the duration of COVID-19 therapies beyond the durations authorized or approved by the Food and Drug Administration (FDA).

When there are no logistical or supply constraints, the COVID-19 Treatment Guidelines Panel (the Panel) recommends prescribing therapies for the prevention or treatment of COVID-19 to any eligible individual as recommended in these Guidelines. However, at times during the pandemic, logistical or supply constraints have limited the availability of therapies. In those cases, the Panel recommends prioritizing the treatment of patients with COVID-19 who are at the highest risk of clinical progression (see Prioritization of Anti-SARS-CoV-2 Therapies for the Treatment of COVID-19 in Nonhospitalized Patients When There Are Logistical Constraints). Providers should use their clinical judgment when prioritizing patients for treatment, including assessing a patient's immunocompromised status, age, and comorbidities.

The sections below outline the Panel's rationale for the recommendations on preventing and managing COVID-19 in people who are immunocompromised. Some of the special considerations for patients who are immunocompromised include the timing of COVID-19 vaccination, the use of pre-exposure prophylaxis (PrEP), the management of immunosuppressive medications, and the strategies for treating COVID-19.

Prevention of COVID-19

Vaccination

The Panel recommends COVID-19 vaccination for all people who are moderately or severely immunocompromised **(AIII)**. Vaccination is the most effective way to prevent serious outcomes and death from SARS-CoV-2 infection, although there are certain special considerations for the timing of vaccination and vaccine responses in people who are immunocompromised. Authorized and approved COVID-19 vaccines in the United States are not live-virus vaccines, and they can be safely administered to patients who are immunocompromised.

The pivotal clinical trials that evaluated the safety and efficacy of the COVID-19 vaccines excluded people who were severely immunocompromised; therefore, the data for this population are less robust.[15,16] Observational data suggest that serological responses to vaccines may be blunted in patients who are immunocompromised.[17,18] Nevertheless, vaccination is still recommended, as it may confer partial protection, including protection from vaccine-induced, cell-mediated immunity.[4] See the Centers for Disease Control and Prevention (CDC) webpage COVID-19 Vaccines for People Who Are Moderately or Severely Immunocompromised for the current COVID-19 vaccination schedule for this population.

Vaccination of Close Contacts

All close contacts of people who are immunocompromised are strongly encouraged to be up to date on vaccination against COVID-19 **(AIII)**. Vaccinating household members, close contacts, and health care workers who provide care for patients who are immunocompromised is important to protect these patients from infection. There is evidence that vaccinated individuals who are infected with SARS-CoV-2 have lower viral loads than unvaccinated individuals, and COVID-19 vaccines are associated with a reduction in the number of SARS-CoV-2 infections not only among vaccinated individuals but also among their household contacts.[19-24]

Vaccine Timing and Anti-SARS-CoV-2 Monoclonal Antibodies

Nonhospitalized patients who are immunocompromised may have received anti-SARS-CoV-2 mAbs

for the treatment of COVID-19. Vaccines can be administered at any time after anti-SARS-CoV-2 mAb treatment.[25] When tixagevimab plus cilgavimab (Evusheld) is being used as PrEP, it should not be administered until at least 2 weeks after vaccination.[25] The use of these anti-SARS-CoV-2 mAbs as PrEP is not a substitute for vaccination.

Vaccine Timing and Immunosuppressive Therapies

If possible, the COVID-19 vaccination series should be completed at least 2 weeks before initiating or resuming immunosuppressive therapies. The timing of the vaccination series should be determined based on the patient's current or planned immunosuppressive therapies, as well as the patient's medical condition and predicted response to the vaccine. Guidance about the timing of COVID-19 vaccination in solid organ transplant, HCT, and cellular immunotherapy candidates can be found in Special Considerations in Solid Organ Transplant, Hematopoietic Cell Transplant, and Cellular Immunotherapy Candidates, Donors, and Recipients. HCT and CAR T-cell recipients who received doses of COVID-19 vaccines prior to or during treatment with an HCT or CAR T-cell therapy should be revaccinated with a primary vaccine series at least 3 months after the transplant or CAR T-cell therapy.[26] The American Society of Hematology and the National Comprehensive Cancer Network have specific guidance about the timing of COVID-19 vaccination around cancer chemotherapy,[26,27] and the American College of Rheumatology also provides guidance for temporarily stopping immunosuppressive regimens during vaccination.[28]

Pre-Exposure Prophylaxis

The Panel recommends using **tixagevimab plus cilgavimab** as SARS-CoV-2 PrEP for adults and adolescents who do not have SARS-CoV-2 infection or recent exposure to an individual with SARS-CoV-2 infection and who are moderately to severely immunocompromised and may have an inadequate immune response to COVID-19 vaccination **(BIIb)**. Information on dosing is available in Prevention of SARS-CoV-2 Infection.

The FDA Emergency Use Authorization (EUA) for tixagevimab plus cilgavimab identifies a broad group of immunocompromised individuals who are eligible for PrEP.[29] Data suggest that some of these individuals are at particularly high risk of inadequate vaccine responses and progression to severe COVID-19 if infected. These individuals include, but are not limited to, those with hematologic malignancies who are receiving active treatment, those who are within 1 year of receiving B cell-depleting agents (e.g., rituximab, ocrelizumab, obinutuzumab, epratuzumab), CAR T-cell therapy recipients, solid organ transplant recipients who are receiving immunosuppressive therapy, those with severe combined immunodeficiencies, and those with HIV and low CD4 counts.[4,9,30-34]

Serologic Testing to Guide Vaccination or Pre-Exposure Prophylaxis Strategies

There is currently insufficient evidence for the Panel to recommend either for or against the use of SARS-CoV-2 serologic testing to assess for immunity or to guide clinical decisions about using COVID-19 vaccines or anti-SARS-CoV-2 mAbs for PrEP. More than 80 SARS-CoV-2 serologic tests, including quantitative, semiquantitative, neutralizing antibody, and point-of-care tests, have been issued EUAs by the FDA to aid in detecting antibodies to SARS-CoV-2.[35] However, these tests are not currently authorized for routine use in making individual medical decisions, and their ability to assess a person's level of immunity or protection from SARS-CoV-2 infection has not been evaluated.[36] Most of these tests have not been calibrated to a reference standard, limiting the comparability and reproducibility of results from different tests.

Management of Patients With COVID-19 Who Are Immunocompromised

Adjusting Chronic Immunosuppressive Therapies

The Panel recommends that decisions regarding stopping or reducing the doses of immunosuppressive drugs in patients with COVID-19 be made in consultation with the appropriate specialists; clinicians should consider factors such as the underlying disease, the specific immunosuppressants being used, the potential for drug-drug interactions, and the severity of COVID-19 **(BIII)**.

Early in the clinical course of COVID-19, the disease is primarily driven by the replication of SARS-CoV-2. Immunosuppressive medications can reduce the host immune responses that suppress viral replication, increasing the risk of prolonged viral shedding and infection.[37,38] Clinicians should consider adjusting the doses of immunosuppressive medications or substituting certain immunosuppressive medications, if possible, to improve the patient's immune response to infection. When making decisions about stopping or reducing the dose of immunosuppressive drugs, clinicians should balance the potential benefit of enhancing the patient's immune response to COVID-19 with the risk of exacerbating the underlying condition. They should also consider the role of immunomodulation in the treatment of COVID-19.

Clinicians should be aware that many immunosuppressive drugs, particularly biologic agents, have long half-lives or prolonged periods of biologic activity. Patients may remain immunosuppressed long after the drugs are stopped. Care should be taken to not stop glucocorticoids abruptly, since this may result in adrenal insufficiency. For medications other than glucocorticoids, decisions about dose adjustments should be made on a case-by-case basis. For example, for some autoimmune diseases, temporary cessation of immunosuppression is often possible, and restarting medications 7 to 14 days after symptom resolution may be appropriate.[28,39]

For solid organ transplant recipients, adjustments to immunosuppressive regimens should be individualized based on disease severity, the risk of graft rejection, the specific immunosuppressants being used, the type of transplant, the time since transplantation, the concentration of immunosuppressants, and the potential for drug-drug interactions.[40] See Special Considerations in Solid Organ Transplant, Hematopoietic Cell Transplant, and Cellular Immunotherapy Candidates, Donors, and Recipients for more information.

Therapeutic Management of Nonhospitalized Patients With COVID-19

The Panel recommends prompt treatment with antiviral agents or anti-SARS-CoV-2 mAbs for nonhospitalized patients with mild to moderate COVID-19 who are immunocompromised **(AIII)**. See Therapeutic Management of Nonhospitalized Adults With COVID-19 to review the Panel's recommendations. Some special considerations for using these therapies in people who are immunocompromised are outlined below.

Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Molnupiravir

In the EPIC-HR trial, ritonavir-boosted nirmatrelvir, when compared with placebo, reduced the risk of hospitalization or death in nonhospitalized, unvaccinated adults who had laboratory-confirmed SARS-CoV-2 infection and a high risk of progressing to severe COVID-19.[41] However, as the trial enrolled very few participants who were immunocompromised, the efficacy of using this drug in this population is unknown.

Because ritonavir-boosted nirmatrelvir is the only highly effective oral antiviral for the treatment of COVID-19, it should be considered for patients who are immunocompromised if there are no potential drug-drug interactions or if the potential interactions can be safely managed. Clinicians should be aware

of drug-drug interactions that may be life- or organ-threatening (see Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir [Paxlovid] and Concomitant Medications).[42] Notably, calcineurin inhibitors (e.g., tacrolimus, cyclosporine A) and mammalian target of rapamycin (mTOR) drugs (e.g., sirolimus, everolimus) have important drug-drug interactions with ritonavir. For this reason, the American Society of Transplantation recommends preferentially using other therapies, such as anti-SARS CoV-2 mAbs or remdesivir, over ritonavir-boosted nirmatrelvir in people who are taking calcineurin inhibitors or mTOR inhibitors.[43]

Ritonavir can inhibit the metabolism of many cancer-directed therapies and should only be given after consulting with specialty pharmacists and other appropriate specialists. Case reports have described reoccurring COVID-19 symptoms and positive SARS-CoV-2 test results in some patients who have completed treatment with ritonavir-boosted nirmatrelvir.[44] There is currently no evidence to support routinely administering longer courses or a second course of ritonavir-boosted nirmatrelvir. People with COVID-19 who are immunocompromised should not delay or avoid taking ritonavir-boosted nirmatrelvir due to concerns about the rebound of symptoms after treatment completion (see Ritonavir-Boosted Nirmatrelvir [Paxlovid]).

In the MOVe-OUT trial, molnupiravir reduced the rate of hospitalization or death in nonhospitalized patients with COVID-19, when compared with placebo.[45] The MOVe-OUT trial enrolled very few participants who were immunocompromised.[46] Although the different treatment options have not been directly compared in clinical trials, the available evidence suggests that molnupiravir has a lower efficacy than the other options (see Molnupiravir). Other COVID-19 therapies should be prioritized over molnupiravir in patients who are immunocompromised.

Remdesivir

Remdesivir was studied in nonhospitalized patients with mild to moderate COVID-19 who were at high risk of progressing to severe disease, and it was shown to be highly effective in reducing the risk of hospitalization and death.[47] However, this trial included few participants who were immunocompromised (see Table 4a). Because remdesivir requires an intravenous infusion for 3 consecutive days, there may be logistical constraints to administering this drug in many settings, but it can be considered for patients who are immunocompromised if other options, such as ritonavir-boosted nirmatrelvir, are not appropriate or available.

Anti-SARS-CoV-2 Monoclonal Antibodies

Clinical trials have demonstrated that anti-SARS-CoV-2 mAb therapy can reduce the risk of hospitalization or death in high-risk patients with COVID-19.[48-51] However, because these trials only enrolled a few patients who were immunocompromised, there is not enough data to determine the efficacy of using anti-SARS-CoV-2 mAbs in this population. Nevertheless, given that a reduced humoral immune response to infection is seen in many patients who are immunocompromised, anti-SARS-CoV-2 mAbs are expected to be effective. Anti-SARS-CoV-2 mAb therapy should be considered for patients who are immunocompromised, especially if significant drug-drug interactions preclude use of ritonavir-boosted nirmatrelvir[40] or logistical constraints prevent the use of remdesivir.

There is insufficient evidence to guide clinical recommendations on using combinations of anti-SARS-CoV-2 mAbs and antiviral drugs. Because the neutralizing activities of some anti-SARS-CoV-2 mAbs may be diminished against certain SARS-CoV-2 variants of concern (VOCs), clinicians should refer to Anti-SARS-CoV-2 Monoclonal Antibodies for guidance on the use of anti-SARS-CoV-2 mAbs against specific circulating VOCs.

COVID-19 Convalescent Plasma

There is insufficient evidence for the Panel to recommend either for or against the use of high-titer CCP

for the treatment of COVID-19 in nonhospitalized patients who are immunocompromised. The FDA has issued an EUA that allows the use of high-titer CCP for the treatment of COVID-19 in nonhospitalized or hospitalized patients who are immunocompromised or who are receiving immunosuppressive treatment.[52] However, the evidence generated from well-designed clinical trials that evaluated the use of CCP for the treatment of nonhospitalized patients is conflicting; these trials enrolled few, if any, patients who were immunocompromised.[53-56]

Some Panel members would use CCP to treat an immunocompromised patient with significant symptoms attributable to COVID-19 and with signs of active SARS-CoV-2 replication and who is having an inadequate response to available therapies. In these cases, clinicians should attempt to obtain high-titer CCP from a vaccinated donor who recently recovered from COVID-19 likely caused by a SARS-CoV-2 variant similar to the variant causing the patient's illness.

Therapeutic Management of Patients Who Are Hospitalized for COVID-19

For most patients with COVID-19 who are immunocompromised, the Panel recommends using antiviral drugs and immunomodulatory therapies at the doses and durations that are recommended for the general population **(AIII)**. See Therapeutic Management of Hospitalized Adults With COVID-19 for more information. The optimal management strategies and treatments for COVID-19 in hospitalized patients who are immunocompromised are unknown, since these individuals were either excluded from or poorly represented in major clinical trials. Nevertheless, clinical experience suggests that many patients who are immunocompromised have the expected responses to standard therapies for COVID-19.

Remdesivir

The optimal duration of treatment with remdesivir in patients who are immunocompromised is unknown. Case reports suggest that the drug can suppress, but does not always eliminate, viral replication in this population.[57,58] Some clinicians may choose to extend the course of antiviral therapy past 5 to 10 days in patients who are immunocompromised, given the risk of prolonged viral replication. Similarly, although remdesivir has not been shown to confer a benefit in patients with more severe respiratory impairment due to COVID-19 (i.e., those who require high-flow nasal cannula [HFNC] oxygen, noninvasive ventilation [NIV], or mechanical ventilation), clinicians may consider using remdesivir along with immunomodulatory therapy in this population of patients who are immunocompromised.

Corticosteroids

The RECOVERY trial reported a survival benefit for dexamethasone in inpatients with COVID-19 who were receiving oxygen, HFNC oxygen, NIV, or mechanical ventilation; however, specific data regarding the subgroup of patients who were immunocompromised are not available.[59]

Patients who are immunocompromised may experience delayed development of favorable adaptive responses and a prolonged period of viral replication, as discussed above. For patients who are immunocompromised, who are receiving minimal levels of conventional oxygen, and who are earlier in the course of COVID-19 (e.g., those with <10 days of symptoms), the preferred approach may be emphasizing supportive care, using antiviral therapy, and avoiding corticosteroids. This strategy may reduce the duration of viral replication and the risk of secondary infections. Dexamethasone should be added if the patient has escalating oxygen requirements.

For patients who are immunocompromised and who were on chronic corticosteroids prior to hospitalization, the optimal dose of dexamethasone for the treatment of COVID-19 is unknown. The recommended dose of dexamethasone is 6 mg, which is equivalent to 40 mg of prednisone. This is the minimum dose of steroid that should be used. Maintenance doses of corticosteroids should be

discontinued while a patient is receiving dexamethasone, and they should be resumed as soon as possible after recovery from COVID-19 or after completion of the course of dexamethasone.

Immunomodulators

Randomized trials have shown that adding interleukin (IL)-6 inhibitors and Janus kinase (JAK) inhibitors to dexamethasone improves clinical outcomes in patients with severe or critical COVID-19. These trials generally excluded patients who were immunocompromised or only included small numbers of these patients.[60-62] For patients who are immunocompromised, the use of these agents may provide a clinical benefit similar to the benefit seen in the general population. However, it is not clear whether augmenting immunomodulation in this population increases the risk of serious bacterial, invasive fungal, or parasitic infections.

For most patients who are immunocompromised, adding IL-6 or JAK inhibitors to dexamethasone is reasonable for those who are hypoxemic and experiencing clinical progression, which follows the Panel's recommendations for the general population (see Therapeutic Management of Hospitalized Adults With COVID-19). However, clinicians should consult with the appropriate specialists to ensure that the risks of additional immunosuppression, including the risks of serious infections, do not outweigh the benefits of additional immunosuppression and that the patient is closely monitored for infections.

COVID-19 Convalescent Plasma

There is insufficient evidence for the Panel to recommend either for or against the use of high-titer CCP for the treatment of COVID-19 in hospitalized patients who are immunocompromised. Three key randomized trials that evaluated the use of CCP for the treatment of COVID-19—RECOVERY, CONCOR-1, and REMAP-CAP—reported no evidence of benefit from CCP in hospitalized patients with COVID-19. However, most of the patients enrolled in these trials were not immunocompromised.[63-65] Some subgroup analyses generated from clinical trials that enrolled patients who were immunocompromised suggested a potential benefit from the use of CCP in this population,[65-67] but subgroup analyses need to be interpreted with caution. Other clinical data from case series, retrospective case-control studies, and meta-analyses have been cited as support for the potential benefit of CCP in patients who are immunocompromised.[68-76] However, the patient populations differed across studies, and the studies had design limitations, making the findings difficult to interpret.

Some Panel members would use CCP to treat an immunocompromised patient with significant symptoms attributable to COVID-19 and with signs of active SARS-CoV-2 replication and who is having an inadequate response to available therapies. In these cases, clinicians should attempt to obtain high-titer CCP from a vaccinated donor who recently recovered from COVID-19 likely caused by a SARS-CoV-2 variant similar to the variant causing the patient's illness.

Therapeutic Management of Patients Who Are Hospitalized for Reasons Other Than COVID-19

People who are immunocompromised and have COVID-19 but were hospitalized for conditions other than COVID-19 should receive the same treatments as nonhospitalized patients **(AIII)**. See Therapeutic Management of Nonhospitalized Adults With COVID-19 for more information.

Therapeutic Management of Hospitalized Patients With Prolonged SARS-CoV-2 Viral Replication

In the absence of evidence, some Panel members would consider using additional treatments in hospitalized patients who are immunocompromised and have ongoing, severe symptoms attributed to viral replication despite the use of other therapies (i.e., remdesivir), because humoral immune responses

may be diminished or absent in this population. These treatments may include using anti-SARS-CoV-2 mAbs (under Emergency Investigational New Drug provisions, if available) that have activity against dominant circulating variants or using high-titer CCP collected from vaccinated donors who were infected with SARS-CoV-2 within the past 6 months.

The optimal management of individuals who are immunocompromised, hospitalized with symptomatic COVID-19, and have prolonged periods of significant viral replication despite the receipt of remdesivir and appropriate immunomodulatory drugs is unknown. Data from the RECOVERY trial of casirivimab plus imdevimab versus placebo suggest that hospitalized patients with COVID-19 who have not developed a humoral immune response (as measured by serologic testing for SARS-CoV-2) received a survival benefit from anti-SARS-CoV-2 mAb therapy.[77]

Special Considerations for Pregnant Individuals Who Are Immunocompromised

Multiple studies have found that pregnant individuals have an increased risk of severe COVID-19 compared to age-matched controls, with increased rates of intensive care unit admission, mechanical ventilation, extracorporeal membrane oxygenation, and death.[78-80] Although hormonally mediated immunomodulation occurs during pregnancy, pregnancy is not a state of systemic immunosuppression. Changes in the immune response to certain infectious pathogens during pregnancy may increase the severity of respiratory illness in pregnant individuals. Physiologic changes, such as reduced pulmonary residual capacity, may also contribute to respiratory disease severity.[81-84] Pregnant people who have underlying immunocompromising conditions or are receiving immunosuppressive medications likely have an even higher risk of severe disease. This patient group should be prioritized for the prevention and treatment of COVID-19.

Prevention

The Panel recommends administering COVID-19 vaccines to pregnant individuals according to the guidelines from the CDC and the Advisory Committee on Immunization Practices (ACIP) **(AI)**. COVID-19 vaccination is strongly recommended for pregnant individuals due to their increased risk for severe disease.[85,86] Vaccination is especially important for pregnant people with concomitant risk factors such as underlying immunocompromising conditions (including those who are receiving immunosuppressive medications), as the risk for severe disease is likely additive.[79] Pregnant individuals who otherwise meet the criteria for PrEP with **tixagevimab plus cilgavimab** should not have this therapy withheld due to their pregnancy status **(AIII)**.

Treatment

Although pregnant patients have been excluded from the majority of the clinical trials that evaluated the use of COVID-19 therapeutics, pregnant patients with COVID-19 can be treated the same as nonpregnant patients, with a few exceptions. Pregnant patients who are immunocompromised or who have other risk factors likely have an even higher risk for severe COVID-19 and should be prioritized for treatment. Providers should refer to the Panel's recommendations in Therapeutic Management of Nonhospitalized Adults With COVID-19 and Therapeutic Management of Hospitalized Adults With COVID-19. Pregnant people who are immunocompromised comprise a heterogeneous group of patients, ranging from those who are mildly immunocompromised to those who are severely immunocompromised. The Panel recommends forming a collaborative, multidisciplinary team to make decisions regarding the evaluation and management of pregnant patients, including the involvement of a transplant or specialty provider, an obstetrician or maternal-fetal medicine specialist, a pediatrics or neonatology specialist, and pharmacy services.

Special Considerations for Children Who Are Immunocompromised

Although the overall risk of critical illness and death related to COVID-19 is lower in children than adults, severe disease does occur, particularly in children with risk factors such as moderate to severe immunocompromising conditions. See Special Considerations in Children for a discussion of the risk factors for severe COVID-19 in children, and see Therapeutic Management of Nonhospitalized Children With COVID-19 for the Panel's framework for assessing a child's risk of progression to severe COVID-19 based on vaccination status, comorbidities, and age.

Prevention

The Panel recommends vaccinating all eligible children against COVID-19 as soon as possible according to the guidelines from the CDC and ACIP **(AI)**. In addition, PrEP with **tixagevimab plus cilgavimab** is authorized by the FDA for children aged ≥12 years and weighing ≥40 kg and recommended by the Panel for those who do not have SARS-CoV-2 infection or recent exposure to an individual with SARS-CoV-2 infection and who are moderately to severely immunocompromised and may have an inadequate immune response to COVID-19 vaccination **(BIIb)**.

Treatment

Most children with mild to moderate COVID-19 will not progress to more severe illness and can be managed with supportive care alone **(AIII)**. Few children, if any, including children aged <18 years who are immunocompromised, have been enrolled in clinical trials of treatments for COVID-19. Therefore, clinicians should be cautious when applying recommendations based on adult data to children. Clinicians need to consider the potential risks and benefits of therapy, the severity of the patient's disease, and underlying risk factors. See Therapeutic Management of Hospitalized Children With COVID-19 and Therapeutic Management of Nonhospitalized Children With COVID-19 for the Panel's treatment recommendations in these scenarios.

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Special Considerations in Adults and Children With Cancer

Last Updated: December 1, 2022

Summary Recommendations

- COVID-19 vaccination remains the most effective way to prevent SARS-CoV-2 infection and should be considered the first line of prevention. The COVID-19 Treatment Guidelines Panel (the Panel) recommends COVID-19 vaccination as soon as possible for everyone who is eligible **(AI)**, including patients with active cancer and patients receiving treatment for cancer **(AIII)**.
- Because vaccine response rates may be lower in people with cancer, specific guidance on administering vaccines to these individuals is provided by the Centers for Disease Control and Prevention. For people with cancer, the Panel recommends following the most current COVID-19 vaccination schedule for people who are moderately or severely immunocompromised.
- Vaccinating household members, close contacts, and health care providers who provide care to patients with cancer is important to protect these patients from infection. All close contacts are strongly encouraged to get vaccinated against COVID-19 as soon as possible **(AIII)**.
- Patients with cancer are at high risk of progressing to serious COVID-19, and they may be eligible to receive anti-SARS-CoV-2 monoclonal antibodies as pre-exposure prophylaxis (PrEP).
- The Panel recommends performing diagnostic molecular or antigen testing for SARS-CoV-2 in patients with cancer who develop signs and symptoms that suggest acute COVID-19 **(AIII)**. The Panel also recommends performing diagnostic molecular testing in asymptomatic patients prior to procedures that require anesthesia and before initiating cytotoxic chemotherapy and long-acting biologic therapy **(BIII)**.
- The recommendations for treating COVID-19 in patients with cancer are the same as those for the general population **(AIII)**. See Therapeutic Management of Nonhospitalized Adults With COVID-19 and Therapeutic Management of Hospitalized Adults With COVID-19 for more information.
- 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)**.
- Clinicians who are treating COVID-19 in patients with cancer should consult a hematologist or oncologist before adjusting cancer-directed medications **(AIII)**.
- Clinicians should pay careful attention to potential overlapping toxicities and drug-drug interactions between drugs used to treat COVID-19 (e.g., ritonavir-boosted nirmatrelvir [Paxlovid], dexamethasone) and cancer-directed therapies, prophylactic antimicrobials, and other medications **(AIII)**.

Each recommendation in the Guidelines receives 2 ratings that reflect the strength of the recommendation and the quality of the evidence that supports it. See Guidelines Development for more information.

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 actively being treated compared to those in remission). In a study that used data from the COVID-19 and Cancer Consortium Registry, patients with cancer who were in remission or who had no evidence of disease had a lower risk of death from COVID-19 than those who were receiving active treatment.[6] It is unclear whether cancer survivors have an increased risk for severe COVID-19 and its complications when compared with people without a

history of cancer.

This section of the COVID-19 Treatment Guidelines focuses on testing for SARS-CoV-2, managing COVID-19 in patients with cancer, and managing cancer-directed therapies during the COVID-19 pandemic. The optimal management and therapeutic approach to COVID-19 in this population has not yet been defined.

COVID-19 Vaccination in Patients With Cancer

The clinical trials that evaluated the COVID-19 vaccines that received Emergency Use Authorizations (EUAs) or approvals from the Food and Drug Administration (FDA) excluded severely immunocompromised patients. The COVID-19 vaccines authorized for use in the United States are not live vaccines; therefore, they can be safely administered to people who are immunocompromised.

Given the effectiveness of COVID-19 vaccines in the general population and the increased risk of severe COVID-19 and mortality in patients with cancer, the COVID-19 Treatment Guidelines Panel (the Panel) recommends COVID-19 vaccination for patients with active cancer and for patients receiving treatment for cancer **(AIII)**.

The Panel also recommends that patients with cancer follow the Centers for Disease Control and Prevention (CDC) schedule for booster doses of COVID-19 vaccines **(AIII)**.

Observational data suggest that serological responses to vaccines may be blunted in patients who are immunocompromised.[7,8] However, vaccination is still recommended for these patients because it may provide partial protection, including protection from vaccine-induced, cell-mediated immunity. See the CDC website COVID-19 Vaccines for People Who Are Moderately or Severely Immunocompromised for the current COVID-19 vaccination schedule for these individuals.

Vaccinating household members, close contacts, and health care providers who provide care to patients with cancer is important to protect these patients from infection. All close contacts are strongly encouraged to get vaccinated as soon as possible **(AIII)**. There is evidence that vaccinated individuals who are infected with SARS-CoV-2 have lower viral loads than unvaccinated individuals[9,10] and that COVID-19 vaccines reduce the incidence of SARS-CoV-2 infections not only among vaccinated individuals but also among their household contacts.[11-13]

The BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) mRNA vaccines contain polyethylene glycol (PEG), whereas the NVX-CoV2373 (Novavax) adjuvanted vaccine and the Ad26.COV2.S (Johnson & Johnson/Janssen) vaccine contain polysorbate 80. Before administering either mRNA vaccine to patients who have experienced a severe anaphylactic reaction to PEG-asparaginase, clinicians should consider testing for a PEG allergy or using the Novavax or Johnson & Johnson/Janssen vaccine with precautions.[14-16] Data on the efficacy of the Novavax vaccine in cancer patients are limited. However, in most situations, the mRNA vaccines or the Novavax vaccine are recommended for primary and booster vaccination over the Johnson & Johnson/Janssen vaccine due to its risk of serious adverse events.[17]

When determining the timing of COVID-19 vaccination in patients with cancer, clinicians should consider the following factors:

- If possible, patients who are planning to receive chemotherapy should receive vaccinations for COVID-19 at least 2 weeks before starting chemotherapy.[18,19]
- In patients with hematologic malignancy who are undergoing intensive chemotherapy (e.g., induction chemotherapy for acute myelogenous leukemia), vaccination should be delayed until

neutrophil recovery.[20]

- Hematopoietic cell and chimeric antigen receptor T cell recipients can be offered COVID-19 vaccination starting at least 3 months after therapy.[19,20]

It is unknown whether the immune response to COVID-19 vaccination can increase the risk of graft-versus-host disease. No immune-related adverse events were reported after COVID-19 vaccination in 2 studies of patients with cancer who received immune checkpoint inhibitors.[21,22]

Decreased immunologic responses to COVID-19 vaccination have been reported in patients who were receiving treatment for solid tumors and hematologic malignancies.[8,23] The type of therapy has been shown to influence the patient's response to vaccination. For example, people with chronic lymphocytic leukemia who were treated with Bruton's tyrosine kinase inhibitors or venetoclax with or without anti-CD20 antibodies had extremely low response rates (16.0% and 13.6%, respectively).[23] In comparison, approximately 80% to 95% of patients with solid tumors showed immunologic responses.[8,24,25] Several observational studies support the use of a third vaccine dose in patients with cancer, even though vaccine failure may still occur.[26-28] See the CDC website COVID-19 Vaccines for People Who Are Moderately or Severely Immunocompromised for guidance on vaccine dosing.

Pre-Exposure Prophylaxis

Vaccination remains the most effective way to prevent SARS-CoV-2 infection and should be considered the first line of prevention. However, some individuals, including some patients with cancer, cannot or may not mount an adequate protective response to COVID-19 vaccines. These patients are at high risk of progressing to severe COVID-19 and may be eligible to receive the anti-SARS-CoV-2 monoclonal antibodies tixagevimab plus cilgavimab (Evusheld) as pre-exposure prophylaxis (PrEP). See Prevention of SARS-CoV-2 Infection for more information.

Testing for SARS-CoV-2 in Patients With Cancer

The Panel recommends performing diagnostic molecular or antigen testing for SARS-CoV-2 in patients with cancer who develop signs and symptoms that suggest acute COVID-19 **(AIII)**.

Patients with cancer who are receiving chemotherapy are at risk of developing neutropenia. The National Comprehensive Cancer Network (NCCN) Guidelines for Hematopoietic Growth Factors categorizes cancer treatment regimens based on the patient's risk of developing neutropenia.[29] A retrospective study suggests that patients with cancer and neutropenia have a higher mortality rate if they develop COVID-19.[30] Studies have reported an increased risk of poor clinical outcomes for patients with COVID-19 in the setting of neutropenia and/or during the perioperative period.[31,32] Because of this, the Panel recommends performing diagnostic molecular testing for SARS-CoV-2 in asymptomatic patients prior to procedures that require anesthesia and before initiating cytotoxic chemotherapy and long-acting biologic therapy **(BIII)**.

General Guidance for Patients With Cancer

Patients with cancer frequently engage with the health care system to receive treatment and supportive care for cancer or treatment-related complications. Nosocomial transmission of SARS-CoV-2 to patients and health care workers has been reported.[33-35] Health care providers and patients should take precautions to reduce the risk of SARS-CoV-2 exposure and infection, including wearing a mask, maintaining a distance of 6 feet from others, and practicing good hand hygiene.[36] Telemedicine can minimize the need for in-person services and reduce the risk of SARS-CoV-2 exposure. For medically or socially vulnerable populations, telemedicine may improve access to providers, but it could worsen disparities if these populations have limited access to technology.

Decisions about treatment regimens, surgery, and radiation therapy for the underlying malignancy should be made on a case-by-case basis, and clinicians should consider the biology of the cancer, the need for hospitalization, the number of clinic visits required, and the anticipated degree of immunosuppression. Additional factors that should be considered include the following:

- If possible, avoid treatment delays for curable cancers that have been shown to have worse outcomes when treatment is delayed (e.g., pediatric acute lymphoblastic leukemia).
- When deciding between equally effective treatment regimens, regimens that can be administered orally or those that require fewer infusions are preferred.[37]
- The potential risks of drug-related lung toxicity (e.g., from using bleomycin or PD-1 inhibitors) must be balanced with the clinical efficacy of alternative regimens or the risk of delaying care.[38]
- Preventing neutropenia can decrease the risk of neutropenic fever and the need for emergency department evaluation and hospitalization. Granulocyte colony-stimulating factor (G-CSF) should be given with chemotherapy regimens that have an intermediate (10% to 20%) or high (>20%) risk of febrile neutropenia.[39]
- Cancer treatment regimens that do not affect the outcomes of COVID-19 in patients with cancer may not need to be altered. In a prospective observational study, receipt of immunotherapy, hormonal therapy, or radiotherapy in the month prior to SARS-CoV-2 infection was not associated with an increased risk of mortality among patients with cancer and COVID-19.[40]
- Radiation therapy guidelines suggest increasing the dose per fraction and reducing the number of daily treatments to minimize the number of hospital visits.[41]

Blood supply shortages will likely continue during the COVID-19 pandemic due to social distancing, cancellation of blood drives, and infection among donors. In patients with cancer, stricter transfusion thresholds for blood products (e.g., red blood cells, platelets) in asymptomatic patients should be considered. At this time, there is no evidence that COVID-19 can be transmitted through blood products.[42]

Febrile Neutropenia

Patients with cancer and febrile neutropenia should undergo diagnostic molecular or antigen testing for SARS-CoV-2 and evaluation for other infectious agents. They should also be given empiric antibiotics.[43] 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. 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.[44,45]

The recommendations for treating COVID-19 in patients with cancer are the same as those for the general population **(AIII)**. See Therapeutic Management of Nonhospitalized Adults With COVID-19 and Therapeutic Management of Hospitalized Adults With COVID-19 for more information. Patients with cancer are at high risk of progressing to severe COVID-19 and are eligible to receive anti-SARS-CoV-2 therapies in the outpatient setting if they develop mild to moderate COVID-19.

In patients with COVID-19 who required supplemental oxygen or mechanical ventilation, the use of dexamethasone has been associated with lower mortality than standard of care treatment alone.[46] 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 not currently recommended for SARS-CoV-2 infection should be administered as part of a clinical trial, since the safety and efficacy of these agents have not been well defined in patients with cancer.

Tocilizumab or baricitinib used in combination with dexamethasone is recommended for some patients with severe or critical COVID-19 who exhibit rapid respiratory decompensation (see Therapeutic Management of Hospitalized Adults With COVID-19).[47-49] The risks and benefits of using dexamethasone in combination with tocilizumab or baricitinib in patients with cancer who recently received chemotherapy is unknown. Because dexamethasone, tocilizumab, and baricitinib are immunosuppressive agents, patients who receive these medications should be closely monitored for secondary infections.

Therapeutic anticoagulation for patients with cancer who are hospitalized for COVID-19 should be managed similarly to anticoagulation for other hospitalized patients. Patients with platelet counts <50,000 cells/μL should not receive therapeutic anticoagulation to treat COVID-19. Clinicians should follow hospital protocols for managing anticoagulation in patients with thrombocytopenia.

The NCCN recommends against using G-CSF and granulocyte-macrophage colony-stimulating factor in patients with cancer and acute COVID-19 who do not have bacterial or fungal infections to avoid the hypothetical risk of increasing inflammatory cytokine levels and pulmonary inflammation.[50,51] Secondary infections (e.g., invasive pulmonary aspergillosis) have been reported in critically ill patients with COVID-19.[52,53]

Decisions about administering cancer-directed therapy to patients with acute COVID-19 and those who are recovering from COVID-19 should be made on a case-by-case basis; clinicians should consider the indication for chemotherapy, the goals of care, and the patient's history of tolerance to the treatment **(BIII)**. The optimal time to initiate or restart cancer-directed therapies after the infection has resolved is unclear. If possible, clinicians should withhold treatment until COVID-19 symptoms have resolved. Prolonged viral shedding may occur in patients with cancer,[2] although it is unknown how this relates to infectious virus and how it impacts outcomes. The decision to restart cancer treatments in this setting should be made on a case-by-case basis. Clinicians who are treating COVID-19 in patients with cancer should consult a hematologist or oncologist before adjusting cancer-directed medications **(AIII)**.

Medication Interactions

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

A 5-day course of ritonavir-boosted nirmatrelvir (Paxlovid) is 1 of the preferred therapies for treating mild to moderate COVID-19 in nonhospitalized patients who are at risk for disease progression. However, this regimen has the potential for significant and complex drug-drug interactions with concomitant medications, primarily due to the ritonavir component of the combination. Boosting with ritonavir, a strong cytochrome P450 (CYP) 3A inhibitor, is required to increase the exposure of nirmatrelvir to a concentration that is effective against SARS-CoV-2. Ritonavir may also increase

concentrations of certain concomitant medications, including certain chemotherapeutic agents and immunotherapies used to treat cancer. Significant increases in the concentrations of these drugs may lead to serious and sometimes life-threatening drug toxicities. Additionally, ritonavir is an inhibitor, inducer, and substrate of various other drug-metabolizing enzymes and drug transporters.

Before prescribing ritonavir-boosted nirmatrelvir, clinicians should carefully review the patient's concomitant medications. Clinicians should refer to resources such as the Liverpool COVID-19 Drug Interactions website, Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications, and the FDA EUA fact sheet for ritonavir-boosted nirmatrelvir for guidance on identifying and managing potential drug-drug interactions. If significant interactions prohibit the concomitant use of ritonavir-boosted nirmatrelvir, another COVID-19 treatment option should be used.

Dexamethasone is commonly used as an antiemetic for patients with cancer and is recommended for the treatment of certain patients with COVID-19 (see Therapeutic Management of Hospitalized Adults With COVID-19). Dexamethasone is a weak to moderate CYP3A4 inducer; therefore, interactions with any CYP3A4 substrates need to be considered.

Special Considerations in Children

Preliminary published reports suggest that pediatric patients with cancer may have milder manifestations of COVID-19 than adult patients with cancer, although larger studies are needed.[54-56] 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.[57] Two publications provide guidance on managing specific malignancies and supportive care and a summary of web links from groups of experts that are relevant to the care of pediatric oncology patients during the COVID-19 pandemic.[57,58] Special considerations for using antiviral drugs in immunocompromised children, including those with malignancy, are available in a multicenter guidance statement.[59]

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

Last Updated: December 1, 2022

Summary Recommendations

Vaccination for COVID-19

- COVID-19 vaccination remains the most effective way to prevent SARS-CoV-2 infection and should be considered the first line of prevention. Given the effectiveness of COVID-19 vaccines in the general population and the increased risk of worse clinical outcomes of COVID-19 in transplant and cellular immunotherapy candidates and recipients, the COVID-19 Treatment Guidelines Panel (the Panel) recommends COVID-19 vaccination for these patients **(AIII)**.
- Because vaccine response rates may be lower in moderately or severely immunocompromised patients, specific guidance on administering vaccines to these individuals is provided by the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices. The Panel recommends following the current COVID-19 vaccination schedule for these patients.
- Vaccinating household members, close contacts, and health care providers who provide care to transplant and cellular immunotherapy candidates and recipients is important to protect these patients from infection. Clinicians should strongly encourage all close contacts to get vaccinated against COVID-19 as soon as possible **(AIII)**.
- Clinicians should strongly encourage all potential organ and hematopoietic cell donors to get vaccinated against COVID-19 **(AI)**.

Pre-Exposure Prophylaxis

- Some transplant candidates or recipients cannot or may not mount an adequate protective response to COVID-19 vaccines. These patients are eligible to receive the anti-SARS-CoV-2 monoclonal antibodies tixagevimab plus cilgavimab (Evusheld) as pre-exposure prophylaxis (PrEP). See Prevention of SARS-CoV-2 Infection for more information.

Potential Transplant and Cellular Immunotherapy Candidates

- The Panel recommends performing diagnostic molecular or antigen testing for SARS-CoV-2 for all potential solid organ transplant, hematopoietic cell transplant (HCT), and cellular immunotherapy candidates with signs and symptoms that suggest acute COVID-19 **(AIII)**. Additional guidance is available from medical professional organizations. See the text below for more information.
- If SARS-CoV-2 is detected or if infection is strongly suspected in a potential transplant or cellular immunotherapy candidate, transplantation or immunotherapy 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 patients **(AIII)**.

Potential Transplant Donors

- The Panel recommends performing diagnostic molecular testing for SARS-CoV-2 and assessing for symptoms of COVID-19 in all potential solid organ transplant and HCT donors prior to donation **(AIII)**. Additional guidance is available from medical professional organizations. See the text below for more information.

Transplant and Cellular Immunotherapy Recipients With COVID-19

- Clinicians should follow the guidelines for evaluating and managing COVID-19 in nontransplant patients when treating transplant and cellular immunotherapy recipients **(AIII)**. See Therapeutic Management of Hospitalized Adults With COVID-19 and Therapeutic Management of Nonhospitalized Adults With COVID-19 for more information.
- Immunocompromised patients with mild to moderate COVID-19 are at high risk of progressing to severe disease and should receive anti-SARS-CoV-2 therapies for treatment.
- Clinicians who are treating COVID-19 in transplant and cellular immunotherapy patients should consult a transplant specialist before adjusting immunosuppressive medications **(AIII)**.

Summary Recommendations, continued
• When treating COVID-19, clinicians should pay careful attention to potential overlapping toxicities and drug-drug interactions between drugs that are used to treat COVID-19 (e.g., ritonavir-boosted nirmatrelvir [Paxlovid]) and immunosuppressants, prophylactic antimicrobials, or other medications **(AIII)**.
Each recommendation in the Guidelines receives 2 ratings that reflect the strength of the recommendation and the quality of the evidence that supports it. See Guidelines Development for more information.

Introduction

Treating COVID-19 in solid organ transplant, hematopoietic cell transplant (HCT), and cellular immunotherapy recipients can be challenging due to the presence of coexisting medical conditions, the potential for transplant-related cytopenias, and the need for chronic immunosuppressive therapy to prevent graft rejection and graft-versus-host disease. Transplant recipients may also have a higher risk of exposure to SARS-CoV-2 given their frequent contact with the health care system. Since immunosuppressive agents modulate several aspects of the host's immune response, the severity of COVID-19 could potentially be affected by the type and intensity of the immunosuppressive effect of the agent, as well as by specific combinations of immunosuppressive agents. Some transplant recipients have medical comorbidities that have been associated with more severe cases of COVID-19 and a greater risk of mortality, which makes the impact of transplantation on disease severity difficult to assess.

The International Society for Heart and Lung Transplantation, the American Society of Transplantation (AST), the American Society for Transplantation and Cellular Therapy, and the European Society for Blood and Marrow Transplantation provide guidance for clinicians who are caring for transplant recipients with COVID-19 and guidance on screening potential donors and transplant or cellular immunotherapy candidates. In addition, the American Society of Hematology offers guidance regarding COVID-19 vaccination for transplant and cellular immunotherapy recipients. This section of the COVID-19 Treatment Guidelines complements these sources and focuses on considerations for managing COVID-19 in solid organ transplant, HCT, and cellular immunotherapy recipients. The optimal management and therapeutic approach to COVID-19 in these populations is unknown. At this time, the procedures for evaluating and managing COVID-19 in transplant recipients are the same as those for nontransplant patients **(AIII)**. See Therapeutic Management of Hospitalized Adults With COVID-19 and Therapeutic Management of Nonhospitalized Adults With COVID-19 for more information. The risks and benefits of each medication that is used to treat COVID-19 may be different for transplant patients and nontransplant patients.

Vaccination for COVID-19

The clinical trials that evaluated the safety and efficacy of the COVID-19 vaccines excluded patients who were severely immunocompromised.[1,2] The currently authorized or approved COVID-19 vaccines are not live vaccines; therefore, they can be safely administered to people who are immunocompromised. However, solid organ transplant recipients have reduced immunological antibody responses following a primary 2-dose or 3-dose series of the mRNA COVID-19 vaccines.[3-6]

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 and recipients **(AIII)**. See the Centers for Disease Control and Prevention (CDC) website COVID-19 Vaccines for People Who Are Moderately or Severely Immunocompromised for the current COVID-19 vaccination schedule for transplant and cellular

immunotherapy recipients.

When determining the timing of COVID-19 vaccination (including booster doses) in solid organ transplant, HCT, and cellular immunotherapy recipients, clinicians should consider the following factors:

- Ideally, solid organ transplant candidates should receive COVID-19 vaccines (either the primary series or booster doses) while they are awaiting transplant.
- In general, the last vaccine should be administered at least 2 weeks prior to a solid organ transplant, or vaccination should be started 1 month after a solid organ transplant.
- In certain situations, it may be appropriate to delay the primary series of vaccinations or booster doses until 3 months after a solid organ transplant, such as when T cell- or B cell-ablative therapy (with antithymocyte globulin or rituximab) is used at the time of transplant.[7]
- Reducing the dose of immunosuppressants and withholding immunosuppressants prior to vaccination **are not recommended**.
- COVID-19 vaccines can be offered as early as 3 months after a patient receives HCT or chimeric antigen receptor T cell therapy, although the vaccines may be less effective in these patients than in the general population.[8-10] If possible, patients who are scheduled to receive cytotoxic or B cell-depleting therapies should receive their COVID-19 vaccination before initiating these therapies or between cycles of these therapies.
- After receiving the primary series of vaccinations or booster doses,[11] people who are immunocompromised should be advised to continue to exercise precautions to reduce their risk of SARS-CoV-2 exposure and infection (e.g., they should wear a mask, maintain a distance of 6 feet from others, and avoid crowds and poorly ventilated spaces).

There is insufficient evidence for the Panel to recommend either for or against the use of SARS-CoV-2 serologic testing to assess for immunity or to guide clinical decisions about using COVID-19 vaccines. For people who received COVID-19 vaccines during treatment with immunosuppressive drugs, it is currently unknown whether revaccination offers a clinical benefit.

Vaccinating household members, close contacts, and health care providers who provide care to transplant and cellular immunotherapy candidates and recipients is important to protect these patients from infection. All close contacts are strongly encouraged to get vaccinated against COVID-19 as soon as possible **(AIII)**. There is evidence that vaccinated individuals who are infected with SARS-CoV-2 have lower viral loads than unvaccinated individuals[12,13] and that COVID-19 vaccines reduce the incidence of SARS-CoV-2 infections not only among vaccinated individuals but also among their household contacts.[14-16] All potential organ and hematopoietic cell donors are also encouraged to get vaccinated against COVID-19 **(AI)**.

Pre-Exposure Prophylaxis

Vaccination remains the most effective way to prevent SARS-CoV-2 infection and should be considered the first line of prevention. However, some individuals, including some transplant candidates and recipients, cannot or may not mount an adequate protective response to COVID-19 vaccines. These patients are at high risk of progressing to severe COVID-19 and may be eligible to receive the anti-SARS-CoV-2 monoclonal antibodies (mAbs) tixagevimab plus cilgavimab (Evusheld) as pre-exposure prophylaxis (PrEP). See Prevention of SARS-CoV-2 Infection for more information.

Assessing SARS-CoV-2 Infection

The risk of transmission of SARS-CoV-2 from donors to candidates is unknown. The probability that a donor or candidate may have SARS-CoV-2 infection can be estimated by considering the epidemiologic

risk, obtaining a clinical history, and testing with molecular techniques. No current testing strategy is sensitive enough or specific enough to totally exclude active infection.

Assessing Transplant and Cellular Immunotherapy Candidates

The Panel recommends performing diagnostic molecular or antigen testing for SARS-CoV-2 in all potential solid organ transplant, HCT, and cellular immunotherapy candidates with signs and symptoms that suggest acute COVID-19 **(AIII)**. The CDC testing algorithm recommends performing additional confirmatory testing with a laboratory-based nucleic acid amplification test (NAAT) when a person who is strongly suspected of having SARS-CoV-2 infection (i.e., a person who is symptomatic) receives a negative result on an antigen test.[17] Shortly before solid organ transplant, HCT, or cellular immunotherapy, all candidates should undergo diagnostic molecular testing for SARS-CoV-2 and assessment for symptoms of COVID-19 **(AIII)**.

Assessing Donors

The Panel recommends performing diagnostic molecular testing for SARS-CoV-2 and assessing for symptoms of COVID-19 in all potential solid organ transplant and HCT donors prior to donation **(AIII)**. Additional guidance is available from medical professional organizations, such as the Organ Procurement and Transplantation Network (OPTN) and the AST.

Living donors should undergo a SARS-CoV-2 NAAT using a specimen collected from the respiratory tract within 3 days of donation. Deceased donors should be tested for SARS-CoV-2 infection using a NAAT with a specimen taken from the upper respiratory tract within 72 hours of death; ideally, the test should be performed as close to organ recovery as possible. Lower respiratory sampling for COVID-19 testing is required for potential lung transplant donors by the United Network for Organ Sharing.[18] The OPTN and AST provide information to help guide the decision-making process when managing solid organ transplant donors with a history of COVID-19.

If SARS-CoV-2 Infection Is Detected or Strongly Suspected in Transplant and Cellular Immunotherapy Candidates

If SARS-CoV-2 is detected or if infection is strongly suspected in a potential transplant or cellular immunotherapy candidate, transplantation or immunotherapy should be deferred, if possible **(BIII)**. The optimal disease-free interval before transplantation or immunotherapy is not known. In this situation, decisions about the appropriate timing for transplantation or cellular immunotherapy should be made on a case-by-case basis. Clinicians should consider both the risk of viral transmission and the risks of delaying or altering therapy, which may include progression of the underlying disease or death.

Transplant Recipients With COVID-19

Solid organ transplant recipients who are receiving immunosuppressive therapy should be considered to be at increased risk for severe COVID-19.[19,20] Initial reports of transplant recipients who were hospitalized with COVID-19 suggest mortality rates of up to 28%.[21-25]

Risk of Graft Rejection

There are concerns that COVID-19 itself may increase the risk for acute rejection. Acute cellular rejection should not be presumed in solid organ transplant recipients without biopsy confirmation, regardless of whether the individual has COVID-19. Similarly, immunosuppressive therapy should be initiated in recipients with or without COVID-19 who have rejection confirmed by a biopsy.[19]

There are limited data on the incidence and clinical characteristics of SARS-CoV-2 infection in HCT[26]

and cellular immunotherapy recipients.[27] 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.[28] 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.[29] Additional factors that have been used to determine the clinical severity of other respiratory viral infections include the degree of cytopenia, the intensity of the conditioning regimen, the graft source, the degree of mismatch, and the need for further immunosuppression to manage graft-versus-host disease. Prolonged viral shedding has been described in solid organ transplant and HCT recipients; this can have implications for preventing infection and for the timing of therapeutic interventions.[30]

Treating COVID-19 in Transplant Recipients

Outpatient transplant recipients who are immunosuppressed or who have certain underlying comorbidities are candidates for several other therapeutic agents that are available through Emergency Use Authorizations (EUAs). See Therapeutic Management of Nonhospitalized Adults With COVID-19 for more information.

When treating hospitalized patients with mild to moderate, symptomatic COVID-19, clinicians should consider administering the therapeutics used in nonhospitalized patients with similar disease severity. Data from a large randomized controlled trial found that a short course of dexamethasone (6 mg once daily for up to 10 days) improved survival in hospitalized people with severe COVID-19 who were mechanically ventilated or who required supplemental oxygen.[31] Tocilizumab or baricitinib used in combination with dexamethasone is recommended for some patients with severe or critical COVID-19 (see Therapeutic Management of Hospitalized Adults With COVID-19).[31-33] Because dexamethasone, tocilizumab, and baricitinib are immunosuppressive agents, patients who receive these medications should be closely monitored for secondary infections.

Therapeutic anticoagulation for transplant recipients who are hospitalized for COVID-19 should be managed similarly to anticoagulation for other hospitalized patients. Patients with platelet counts <50,000 cells/μL should not receive therapeutic anticoagulation to treat COVID-19. Clinicians should follow hospital protocols for managing anticoagulation in patients with thrombocytopenia.

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

Concomitant Medications

Clinicians should pay special attention to the potential for drug-drug interactions and overlapping toxicities between treatments for COVID-19 and concomitant medications, such as immunosuppressants that are used to prevent allograft rejection and antimicrobials that are used to prevent or treat opportunistic infections. 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.[22]

Clinicians who are treating COVID-19 in transplant and cellular immunotherapy patients should consult a transplant specialist before adjusting immunosuppressive medications **(AIII)**.

Drug-Drug Interactions

Calcineurin inhibitors (e.g., cyclosporine, tacrolimus) and mammalian target of rapamycin (mTOR) inhibitors (e.g., everolimus, sirolimus), which are commonly used to prevent allograft rejection, have narrow therapeutic indices. Medications that inhibit or induce cytochrome P450 (CYP) enzymes or P-glycoprotein may put patients who receive these drugs at risk of clinically significant drug-drug interactions, increasing the need for therapeutic drug monitoring and the need to assess for signs of toxicity or rejection.[34]

A 5-day course of ritonavir-boosted nirmatrelvir (Paxlovid) is 1 of the preferred therapies for treating mild to moderate COVID-19 in nonhospitalized patients who are at risk for disease progression. However, this regimen has the potential for significant and complex drug-drug interactions with concomitant medications, primarily due to the ritonavir component of the combination. Boosting with ritonavir, a strong CYP3A inhibitor, is required to increase the exposure of nirmatrelvir to a concentration that is effective against SARS-CoV-2. Ritonavir may also increase concentrations of certain concomitant medications, including calcineurin and mTOR inhibitors, during the treatment course and for ≥3 days after ritonavir is discontinued. Significant increases in the concentrations of these drugs may lead to serious and sometimes life-threatening drug toxicities.

For nonhospitalized transplant patients who are receiving calcineurin or mTOR inhibitors as part of their antirejection regimen, the AST recommends either an anti-SARS-CoV-2 mAb or remdesivir as the first-line therapy.[35] If these drugs are not available or feasible to use, ritonavir-boosted nirmatrelvir may be used with caution. Ritonavir-boosted nirmatrelvir should only be used when close monitoring of the patient is possible, and clinicians should consult with transplant specialists during the treatment course. General guidance for coadministering ritonavir-boosted nirmatrelvir with concomitant medications includes temporarily withholding certain immunosuppressive agents (e.g., tacrolimus, everolimus, sirolimus) or reducing the dosage of certain immunosuppressive agents (e.g., cyclosporine), monitoring the patient closely for toxicities, and performing therapeutic drug monitoring (if possible) during and after the treatment course of ritonavir-boosted nirmatrelvir.[35,36]

Some small case series have reported success in using these recommendations to manage patients;[37,38] however, cases of significant toxicities due to supratherapeutic tacrolimus concentrations have also been reported.[39] Therapeutic drug monitoring should be used to guide the process of reintroducing or modifying the doses of calcineurin and mTOR inhibitors in patients who have completed a course of ritonavir-boosted nirmatrelvir. Clinicians should also consult with a specialist who has experience with dose management. Clinicians should take additional precautions when treating transplant recipients who are also receiving other concomitant medications (e.g., certain triazole antifungals) that may interact with ritonavir, the immunosuppressants, or both. The extent and significance of multiple drug-drug interactions are much more complex and unpredictable.

Clinicians should refer to resources such as the Liverpool COVID-19 Drug Interactions website, Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications, and the EUA fact sheet on ritonavir-boosted nirmatrelvir for guidance on identifying and managing potential drug-drug interactions. If significant interactions prohibit the concomitant use of ritonavir-boosted nirmatrelvir, another COVID-19 treatment option should be used (see Therapeutic Management of Nonhospitalized Adults With COVID-19).

Among the drugs that are commonly used to treat hospitalized patients with COVID-19, dexamethasone is a moderate inducer of CYP3A4, and interleukin-6 inhibitors may lead to increased metabolism of

CYP substrates. Clinicians should closely monitor the serum concentrations of calcineurin and mTOR inhibitors when these drugs are used.

Additional details about the adverse effects and drug-drug interactions of antiviral medications (including anti-SARS-CoV-2 antibody products) and immune-based therapies for COVID-19 are noted in Tables 4e and 5f.

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Special Considerations in Pregnancy

Last Updated: September 26, 2022

Summary Recommendations

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 detailing 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.
- General 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
- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** withholding COVID-19 treatments or vaccination from pregnant or lactating individuals specifically because of pregnancy or lactation **(AIII)**.
- In general, the therapeutic management of pregnant patients with COVID-19 should be the same as for nonpregnant patients, with a few exceptions **(AIII)**. Notable exceptions include:
  - The Panel **recommends against** the use of **molnupiravir** for the treatment of COVID-19 in pregnant patients unless there are no other options and therapy is clearly indicated **(AIII)**.
  - There is insufficient evidence for the Panel to recommend either for or against the use of therapeutic anticoagulation in pregnant patients with COVID-19 who do not have evidence of venous thromboembolism. See Antithrombotic Therapy in Patients With COVID-19 for more information.
- For details regarding therapeutic recommendations and pregnancy considerations, see Therapeutic Management of Nonhospitalized Adults With COVID-19, Therapeutic Management of Hospitalized Adults With COVID-19, and the individual drug sections.
- There are limited data on the use of COVID-19 therapeutic agents in pregnant and lactating people. When making decisions about treatment, pregnant or lactating people and their clinical teams should use a shared decision-making process that takes several factors into consideration, including the severity of COVID-19, the risk of disease progression, and the safety of specific medications for the fetus, infant, or pregnant or lactating individual. For detailed guidance on using COVID-19 therapeutic agents during pregnancy, refer to the pregnancy considerations subsections in Antivirals (Including Antibody Products) and Immunomodulators.
- The decision to feed the infant breast milk while the lactating 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 risk of pausing lactation on the future of breast milk delivery to the infant.

Each recommendation in the Guidelines receives 2 ratings that reflect the strength of the recommendation and the quality of the evidence that supports it. See Guidelines Development for more information.

Epidemiology of COVID-19 in Pregnancy

Although the overall risk of severe illness is low, pregnant people with COVID-19 are at a higher risk of severe disease than nonpregnant people. After adjustments have been made for age, race/ethnicity, and underlying medical conditions, pregnant women have 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).[1]

An ongoing systematic review and meta-analysis of 149 studies also described increased odds of ICU admission and mechanical ventilation among pregnant and recently pregnant patients with COVID-19 when compared with nonpregnant patients of reproductive age.[2,3] Compared with pregnant women and recently pregnant women without COVID-19, pregnant women with COVID-19 were at a higher risk of preterm birth and stillbirth.

Obstetric and Perinatal Outcomes in Patients With COVID-19

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.[4] The data suggested that adverse perinatal outcomes were more common in patients with severe or critical disease than in asymptomatic patients with SARS-CoV-2 infection, including an increased incidence of cesarean delivery (59.6% vs. 34.0% of patients; aRR 1.57; 95% CI, 1.30–1.90), hypertensive disorders of pregnancy (40.4% vs. 18.8%; aRR 1.61; 95% CI, 1.18–2.20), and preterm birth (41.8% vs. 11.9%; aRR 3.53; 95% CI, 2.42–5.14). The perinatal outcomes for those with mild to moderate illness were similar to those observed among asymptomatic patients with SARS-CoV-2 infection.

Among 1,249,634 delivery hospitalizations in the United States from March 2020 through September 2021, women with COVID-19 had an increased risk of stillbirth, which was defined as fetal death at >20 weeks' gestation (aRR 1.90; 95% CI, 1.69–2.15).[5] The risk of stillbirth was higher during the time period that the Delta variant was the dominant variant in the United States (aRR 4.04; 95% CI, 3.28–4.97) than during the pre-Delta period (aRR 1.47; 95% CI, 1.27–1.71).

A retrospective cohort analysis collected data from 14,104 pregnant or recently postpartum individuals who delivered at U.S. hospitals that participated in the Gestational Research Assessments for COVID-19 (GRAVID) study.[6] Compared with pregnant individuals who did not have SARS-CoV-2 infection, patients with COVID-19 during pregnancy had an increased risk of meeting the composite endpoint of maternal death or severe morbidity related to hypertensive disorders of pregnancy, postpartum hemorrhage, or infection. Eighty percent of the patients in this cohort tested positive for SARS-CoV-2 infection during the third trimester. The primary composite endpoint occurred in 13.4% of patients with COVID-19 during pregnancy or within 6 weeks postpartum and in 9.4% of those without COVID-19 (aRR 1.41; 95% CI, 1.23–1.61). When compared with those who did not have a positive SARS-CoV-2 test result, pregnant patients who had SARS-CoV-2 infection prior to 28 weeks' gestation had a subsequent increased risk of fetal/neonatal death (aRR 1.97; 95% CI, 1.01–3.85), preterm birth at <37 weeks (aRR 1.29; 95% CI, 1.02–1.63), and hypertensive disorders of pregnancy with delivery at <37 weeks' gestation (aRR 1.74; 95% CI, 1.19–2.55). There were no significant differences between these groups of patients in the risk of preterm birth at <34 weeks, any major congenital abnormalities, or a size for gestational age of less than the fifth or tenth percentiles. There were also no significant differences between these groups in the rates of gestational hypertension overall or preeclampsia with severe features.[7] These data suggest that those with SARS-CoV-2 infection early in gestation may also have an increased risk of subsequent adverse pregnancy outcomes.

Vertical Transmission of COVID-19

Although vertical transmission of SARS-CoV-2 is possible, current data suggest that it is rare.[8] 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).

Data collected by the Centers for Disease Control and Prevention (CDC) as part of the Surveillance for Emerging Threats to Mothers and Babies Network showed that among 4,038 infants born to people with COVID-19, for whom laboratory testing information was available and who were tested during the delivery hospitalization, 227 infants (5.6%) had positive PCR results for SARS-CoV-2.[9]

The published data to date were largely collected prior to the emergence of the Omicron variants. The risk of vertical transmission may vary based on viral dynamics and the transmissibility of the circulating variants in a community; however, the variant-specific factors that are associated with vertical transmission have not been determined. For additional information on vertical transmission and infants born to people with SARS-CoV-2 infection, see Special Considerations in Children.

Racial and Ethnic Disparities Among Pregnant People With COVID-19

Between January 22 and June 7, 2020, 8,207 pregnant women with COVID-19 were reported to CDC. Among these women, 46% were reported to be Hispanic and 22% were reported to be Black. Those proportions were higher than the proportions 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.[10] These disparities have been reported in the nonpregnant population as well.[11] It is important to note that these disparities are related to social determinants of health, current and historic inequities in access to health care and other resources, and structural racism. The American College of Obstetricians and Gynecologists (ACOG) has published guidance on addressing health equity during the COVID-19 pandemic.

Prevention of 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. Non-pharmacologic measures include practicing physical distancing, washing hands regularly, and wearing a face covering as per guidance from the CDC.

COVID-19 Vaccines

Pregnant people should be counseled about the benefits of COVID-19 vaccination, which include a decreased risk of severe disease and hospitalization for the pregnant person and a decreased risk of hospitalization for the infant in the first 6 months of life.[12] The Society for Maternal-Fetal Medicine (SMFM), the ACOG, and the CDC recommend that all eligible persons, including pregnant and lactating individuals and those who are planning to become pregnant, receive a COVID-19 vaccine or vaccine series. This includes booster doses, if the person is eligible. The CDC has published up-to-date guidance regarding COVID-19 vaccination, including guidance for administering vaccines to pregnant and lactating individuals. COVID-19 vaccines can be administered regardless of trimester and in concert with other vaccines that are recommended during pregnancy.[13]

Pregnant people were not included in the initial COVID-19 vaccine studies. However, there is a growing body of observational data that supports the efficacy and safety of administering COVID-19 vaccines to this population. At this time, the mRNA COVID-19 vaccines and the recently authorized Novavax vaccine are preferred over the Johnson & Johnson/Janssen vaccine for all eligible individuals, including pregnant and lactating people.[13,14] For the most up-to-date clinical recommendations, see the CDC

guidelines on using COVID-19 vaccines. The ACOG and SMFM provide guidance for counseling pregnant and lactating patients about COVID-19 vaccination.[13,15]

Efficacy

A prospective cohort study of 131 subjects at 2 academic medical centers compared the immunogenicity and reactogenicity of the mRNA COVID-19 vaccines in pregnant and lactating women and nonpregnant controls. The study also compared vaccine-generated immunity to the immune response to natural SARS-CoV-2 infection among pregnant participants.[16] Maternal immunoglobulin (Ig) G antibody levels were similar after vaccination in pregnant and lactating women and in nonpregnant controls, and the antibody response did not differ by trimester of vaccination. There were significantly higher levels of antibodies in vaccinated pregnant women compared with pregnant women who had had natural SARS-CoV-2 infection during the previous 4 to 12 weeks. In addition, maternal receipt of a COVID-19 vaccine series was protective against infant hospitalization with COVID-19 in the first 6 months of life.[12]

Antibody Transfer to the Neonate

The available data indicate that vaccine-derived antibodies are passively transferred to the neonate during pregnancy and lactation.[17] A case control study that was conducted at 20 pediatric hospitals in 17 states in the United States from July 1, 2021, to January 17, 2022, assessed the relationship between maternal vaccination with a 2-dose mRNA COVID-19 vaccine during pregnancy and pediatric hospitalization for COVID-19.[12] In this study, 379 infants aged <6 months were hospitalized. One hundred seventy-six of these infants had COVID-19 and were considered case infants; the remaining 203 infants did not have COVID-19 and were considered control infants. Sixteen percent of the mothers of the case infants had received 2 COVID-19 vaccine doses during pregnancy compared with 32% of the mothers of control infants. Maternal completion of a 2-dose primary mRNA COVID-19 vaccination series during pregnancy led to a decrease in the number of infant hospitalizations for COVID-19 during the first 6 months of life (61% decrease; 95% CI, 31% to 78%). There were no statistically significant differences between the case infants and control infants in the presence of underlying medical conditions or the occurrence of premature birth. Of the 43 case infants who were admitted to the ICU, 88% had mothers who were unvaccinated. These data further support the CDC's recommendation for COVID-19 vaccination in people who are pregnant, breastfeeding, or trying to become pregnant or who might become pregnant in the future.[18]

Safety

A study that used data from 3 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.

The CDC is enrolling pregnant patients in the v-safe COVID-19 Vaccine Pregnancy Registry to collect and analyze data related to COVID-19 vaccination in pregnant people and their infants. As of May 2, 2022, 23,779 pregnant people in the United States have been enrolled. Surveillance data from 3,958 pregnant patients who were enrolled in the registry showed that, among 827 people who completed their pregnancies, there were no 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.[19]

Pre-Exposure Prophylaxis With Anti-SARS-CoV-2 Monoclonal Antibodies

Pregnancy does not preclude the use of anti-SARS-CoV-2 monoclonal antibodies (mAbs) as pre-

exposure prophylaxis (PrEP). Similar to nonpregnant patients, pregnant patients qualify for PrEP with anti-SARS-CoV-2 mAbs if they are unable to mount an adequate immune response to vaccination or they cannot receive a COVID-19 vaccine due to the potential for a severe reaction to the vaccine or its components. As IgG mAbs, the authorized anti-SARS-CoV-2 mAbs would be expected to cross the placenta. There are no data on the use of these mAbs in pregnant patients; however, other IgG products have been safely used in pregnant people when their use is indicated. Therefore, authorized anti-SARS-CoV-2 mAbs should not be withheld during pregnancy.

Managing COVID-19 in Pregnancy

As in nonpregnant patients, SARS-CoV-2 infection can present in pregnant patients 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. 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

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 makes it difficult to provide evidence-based recommendations on the use of anti-SARS-CoV-2 therapies in these vulnerable patients and potentially limits their treatment options. When possible, pregnant and lactating individuals should not be excluded from clinical trials of COVID-19 therapeutic agents or vaccines.

The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** withholding COVID-19 treatments from pregnant or lactating individuals specifically because of pregnancy or lactation **(AIII)**. For details regarding therapeutic recommendations and pregnancy considerations, see General Management of Nonhospitalized Adults With Acute COVID-19 and the individual drug sections.

Utilizing a shared decision-making process and acknowledging the limitations of available data in pregnancy, the pregnant patient and the clinical team should consider the safety of the medication for the pregnant or lactating individual and the fetus, as well as the severity of maternal disease. For detailed guidance on the use of COVID-19 therapeutic agents during pregnancy, refer to the pregnancy considerations subsections in Antivirals (Including Antibody Products) and Immunomodulators.

In general, the therapeutic management of pregnant patients with COVID-19 should be the same as for nonpregnant patients, with a few exceptions **(AIII)**. Notable exceptions include:

- The Panel **recommends against** the use of **molnupiravir** for the treatment of COVID-19 in

pregnant patients unless there are no other options and therapy is clearly indicated **(AIII)**. Fetal toxicity has been reported in animal studies of molnupiravir. However, when other therapies are not available, pregnant people with COVID-19 who are at high risk of progressing to severe disease may reasonably choose molnupiravir therapy after being fully informed of the risks, particularly if they are beyond the time of embryogenesis (i.e., >10 weeks' gestation). There is currently a lack of data on the use of molnupiravir in lactating people, and molnupiravir may cause adverse effects in infants who are exposed to the drug through breastfeeding. Because of this, the Food and Drug Administration Emergency Use Authorization for molnupiravir states that lactating people should not breastfeed their infants during treatment with molnupiravir and for 4 days after the final dose. Pumping and discarding breast milk to maintain supply during this time is recommended.

- Pregnant patients were not included in most of the clinical trials that evaluated therapeutic anticoagulation in the setting of COVID-19, and there is a potential for increased maternal risks if bleeding occurs during pregnancy. Therefore, there is insufficient evidence for the Panel to recommend either for or against the use of therapeutic anticoagulation in pregnant patients with COVID-19 who do not have evidence of venous thromboembolism.

Timing of Delivery

The 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 people who had suspected or confirmed COVID-19 early in pregnancy and who recovered, no alteration to the usual timing of delivery is indicated.

Post-Delivery

Therapeutic management in postpartum patients should follow guidelines for nonpregnant patients. However, the use of anticoagulation therapy in the immediate postpartum period should be individualized, as there may be an increased risk of bleeding, especially after an operative 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.[20] 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 risk of pausing lactation on the future of breast milk delivery to the infant.

Specific guidance on the post-delivery management of infants born to individuals with known or suspected SARS-CoV-2 infection, including breastfeeding recommendations, is provided by the CDC and the American Academy of Pediatrics and in Special Considerations in Children.

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Influenza and COVID-19

Last Updated: September 30, 2022

Summary Recommendations

Influenza Vaccination

- People with acute COVID-19 should receive an inactivated influenza vaccine **(BIII)**.
  - Clinicians should consider deferring influenza vaccination for symptomatic patients with COVID-19 until these patients are no longer moderately or severely ill and have completed their COVID-19 isolation period.
  - Clinicians should advise people with asymptomatic SARS-CoV-2 infection or mild COVID-19 symptoms to seek influenza vaccination when they no longer require isolation. They can be vaccinated sooner if they are in a health care setting for other reasons.
- An influenza vaccine and a COVID-19 vaccine may be administered concurrently at different injection sites. See the recommendations from the Centers for Disease Control and Prevention (CDC) and the Advisory Committee on Immunization Practices for more information.

Diagnosis of Influenza and COVID-19 When Influenza Viruses and SARS-CoV-2 Are Cocirculating

- Only testing can distinguish between SARS-CoV-2 and influenza virus infections and identify SARS-CoV-2 and influenza virus coinfection.
- The COVID-19 Treatment Guidelines Panel (the Panel) recommends influenza testing in addition to SARS-CoV-2 testing in outpatients with acute respiratory illness if the results will change the clinical management strategy for the patient (e.g., administering antiviral treatment for influenza) **(BIII)**.
- The Panel recommends testing for both viruses in all hospitalized patients with acute respiratory illness **(AIII)**.
- Clinicians should consider testing patients for other pathogens based on the specific clinical circumstances. Additional testing for bacterial pathogens is important for patients with influenza and clinical signs that suggest bacterial superinfections, especially for patients who are immunocompromised or intubated.
- See the CDC webpage Information for Clinicians on Influenza Virus Testing and the Infectious Diseases Society of America (IDSA) clinical practice guidelines for more information.

Antiviral Treatment of Influenza When Influenza Viruses and SARS-CoV-2 Are Cocirculating

- Antiviral treatment for influenza is the same for all patients regardless of SARS-CoV-2 coinfection **(AIII)**.
  - For information on using antiviral drugs to treat influenza in hospitalized and nonhospitalized patients, see the CDC and IDSA recommendations.
  - There are no clinically significant drug-drug interactions between the antiviral agents or immunomodulators that are used to prevent or treat COVID-19 and the antiviral agents that are used to treat influenza.
- The Panel recommends that hospitalized patients who are suspected of having either influenza or COVID-19 be started on empiric treatment for influenza with **oseltamivir** as soon as possible and without waiting for influenza test results **(AIIb)**.
  - Antiviral treatment for influenza can be stopped when influenza has been ruled out by the results of a nucleic acid detection assay. The assay should be performed on upper respiratory tract specimens for nonintubated patients and on both upper and lower respiratory tract specimens for intubated patients.

Each recommendation in the Guidelines receives 2 ratings that reflect the strength of the recommendation and the quality of the evidence that supports it. See Guidelines Development for more information.

Introduction

Influenza activity during the 2021 to 2022 influenza season in the United States occurred in 2 waves and extended from November 2021 through mid-June 2022.[1] The overall severity of the 2021 to 2022 season was lower than the severity of seasonal influenza epidemics that occurred before the emergence of SARS-CoV-2. However, in some countries in the southern hemisphere (e.g., Australia), the levels of

influenza activity observed during the 2021 to 2022 season were similar to pre-COVID-19 pandemic levels.[2,3]

Clinicians should monitor local influenza and SARS-CoV-2 activities during influenza season to inform the evaluation and management of patients with acute respiratory illness. This can be done by tracking local and state public health surveillance data, assessing the results of testing performed at health care facilities, and reviewing the Centers for Disease Control and Prevention (CDC) Weekly U.S. Influenza Surveillance Report.

Influenza Vaccination

For Patients With Acute COVID-19 or Those Recovering From COVID-19

The Advisory Committee on Immunization Practices (ACIP) recommends offering an influenza vaccine by the end of October to all people aged ≥6 months in the United States.[4] People with acute COVID-19 should receive an inactivated influenza vaccine **(BIII)**.

There are currently no data on the safety, immunogenicity, or efficacy of influenza vaccines in patients with mild COVID-19 or those who are recovering from COVID-19. The safety and efficacy of vaccinating people who have mild illnesses from other etiologies have been documented.[5] Clinicians should consider deferring influenza vaccination for symptomatic patients with COVID-19 until these patients are no longer moderately or severely ill and have completed their COVID-19 isolation period. People with asymptomatic SARS-CoV-2 infection or mild COVID-19 symptoms should seek influenza vaccination when they no longer require isolation. They can be vaccinated sooner if they are in a health care setting for other reasons.

It is not known whether administering dexamethasone or other immunomodulatory therapies to patients with severe COVID-19 will affect the immune response to an influenza vaccine. Nevertheless, as long as influenza viruses are circulating, people with COVID-19 should receive an influenza vaccine once they have substantially improved or recovered from COVID-19. See the influenza vaccine recommendations from the CDC, the ACIP, and the American Academy of Pediatrics.

Coadministration of COVID-19 Vaccines and Influenza Vaccines

Although there are currently limited data on coadministering COVID-19 vaccines and influenza vaccines, these vaccines may be administered concurrently at different injection sites.[6-8] Providers and patients should be aware of the potential for increased reactogenicity when both vaccines are administered concurrently. See the recommendations from the CDC and the ACIP for more information.

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 young infants, adults of advanced age, and patients who are immunosuppressed. Complications of influenza and COVID-19 can be similar, but the onset of influenza complications and severe disease typically occurs within a week of illness onset, whereas the onset of severe COVID-19 usually occurs in the second week of illness.

Because of the overlap in signs and symptoms, when SARS-CoV-2 and influenza viruses are cocirculating, diagnostic testing for both viruses is needed to distinguish between SARS-CoV-2 and influenza virus and to identify coinfection in people with an acute respiratory illness. Coinfection with influenza virus and SARS-CoV-2 has been described in case reports and case series,[9-13] but it is

uncommon.[14] Observational studies have reported greater disease severity in patients with influenza virus and SARS-CoV-2 coinfection than in patients with SARS-CoV-2 infection alone.[15,16]

Testing for SARS-CoV-2 and Influenza

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 if the results will change the clinical management strategy for the patient (e.g., administering antiviral treatment for influenza) **(BIII)**. SARS-CoV-2 testing and influenza testing should be performed in all patients who are hospitalized with an acute respiratory illness (see Testing for SARS-CoV-2 Infection) **(AIII)**. Several multiplex molecular assays and multiplex antigen assays that detect SARS-CoV-2 and influenza A and B viruses have received Food and Drug Administration Emergency Use Authorizations or De Novo classifications and can provide results in 15 minutes to 8 hours using a single respiratory specimen.[17,18] For more information, see the CDC webpage Information for Clinicians on Influenza Virus Testing and the recommendations from the Infectious Diseases Society of America (IDSA) on the use of influenza tests and the interpretation of test results.[19]

Treating Influenza With Antiviral Agents

Antiviral treatment for influenza is the same for all patients regardless of SARS-CoV-2 coinfection **(AIII)**. There are no clinically significant drug-drug interactions between the antiviral agents or immunomodulators that are used to prevent or treat COVID-19 and the antiviral agents that are used to treat influenza. The IDSA recommends administering antiviral treatment for influenza to all hospitalized patients with influenza.[19]

The Panel recommends that hospitalized patients who are suspected of having either influenza or COVID-19 be started on empiric treatment for influenza with **oseltamivir** as soon as possible and without waiting for influenza test results **(AIIb)**. Oseltamivir has no activity against SARS-CoV-2.[20] The standard dose of oseltamivir is well absorbed even in critically ill patients. For patients who cannot tolerate oral or enterically administered oseltamivir (e.g., because of gastric stasis, malabsorption, or gastrointestinal bleeding), intravenous peramivir is an option.[19] There are no data on the activity of peramivir against SARS-CoV-2.

See the CDC webpage Influenza Antiviral Medications: Summary for Clinicians for clinical algorithms for using antiviral agents in patients with suspected or laboratory-confirmed influenza, including pregnant people and other people who are at high risk for influenza complications. The IDSA clinical practice guidelines also provide recommendations on using antiviral agents to treat influenza, and the American Academy of Pediatrics provides recommendations on the antiviral treatment of influenza in children.

When the result of an influenza nucleic acid detection assay from an upper respiratory tract specimen is negative in a patient who is receiving antiviral treatment for influenza:

- *In a patient who is not intubated:* Antiviral treatment for influenza can be stopped.
- *In a patient who is intubated:* Antiviral treatment for influenza should be continued, and if a lower respiratory tract specimen (e.g., endotracheal aspirate) can be safely obtained, it should be tested using an influenza nucleic acid detection assay. If the lower respiratory tract specimen is also negative, antiviral treatment for influenza can be stopped.

COVID-19 Treatment Considerations for Hospitalized Patients With Suspected or Confirmed Influenza Virus Coinfection

Corticosteroids, which are used to treat patients with severe COVID-19, may prolong influenza viral

replication and viral RNA detection and may be associated with poor outcomes for influenza.[19,21] Currently, no data are available on the use of corticosteroids in patients with SARS-CoV-2 and influenza virus coinfection. However, because dexamethasone has demonstrated substantial benefits for patients with COVID-19 who require supplemental oxygen, the benefits of using corticosteroids in patients with severe SARS-CoV-2 and influenza virus coinfection likely outweigh any potential harms.

Remdesivir does not have activity against influenza viruses. There are no known drug-drug interactions between remdesivir and oseltamivir. Therefore, remdesivir may be safely coadministered with oseltamivir in patients with COVID-19 and suspected or laboratory-confirmed influenza.

Although severe influenza may be associated with a dysregulated innate immune response, there are no data on the use of immunomodulatory therapies, such as interleukin-6 inhibitors (e.g., tocilizumab, sarilumab) or Janus kinase inhibitors (e.g., baricitinib, tofacitinib), for the treatment of severe influenza. There are also no data on the effect these therapies may have on influenza viral replication. Because these immunomodulators have demonstrated a clinical benefit in certain patients with COVID-19, clinicians should consider engaging in a shared decision-making process on the use of these drugs with patients who have been diagnosed with COVID-19 and who have suspected or laboratory-confirmed influenza.

Observational studies have reported that co-occurrence of community-acquired secondary bacterial pneumonia appears to be infrequent in people with COVID-19; it is more common in people who have influenza.[22-27] Typical bacterial causes of community-acquired pneumonia with severe influenza are *Staphylococcus aureus* (both methicillin-resistant *S. aureus* [MRSA] and methicillin-susceptible *S. aureus* [MSSA]), *Streptococcus pneumoniae*, and group A *Streptococcus*.[19]

Patients with COVID-19 who develop new respiratory symptoms with or without fever or respiratory distress and who do not have a clear diagnosis should be evaluated for the possibility of nosocomial influenza.

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Special Considerations in People With HIV

Last Updated: May 2, 2022

Summary Recommendations

Prevention of COVID-19

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends that people with HIV receive COVID-19 vaccines regardless of their CD4 T lymphocyte (CD4) cell count or HIV viral load, because the potential benefits outweigh the potential risks **(AIII)**.
- The Advisory Committee on Immunization Practices recommends that people with advanced or untreated HIV who received a 2-dose series of an mRNA COVID-19 vaccine should receive a third dose of that vaccine at least 28 days after the second dose. Advanced HIV is defined as people with CD4 counts <200 cells/mm^3, a history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV.
- People with advanced or untreated HIV who do not have SARS-CoV-2 infection and who have not been recently exposed to SARS-CoV-2 are eligible to receive the anti-SARS-CoV-2 monoclonal antibodies (mAbs) tixagevimab plus cilgavimab as pre-exposure prophylaxis (PrEP). See Prevention of SARS-CoV-2 Infection for details.
- Two anti-SARS-CoV-2 mAb combinations, **bamlanivimab plus etesevimab** and **casirivimab plus imdevimab**, have received Emergency Use Authorizations from the Food and Drug Administration for post-exposure prophylaxis (PEP). However, the Panel **recommends against** their use in patients with COVID-19, including in people with HIV, because the Omicron variant is currently the dominant SARS-CoV-2 variant in the United States, and it is not susceptible to these anti-SARS-CoV-2 mAbs **(AIII)**.

Diagnosis of COVID-19

- The Panel recommends using the same approach for diagnosing SARS-CoV-2 infection in people with HIV as in people without HIV **(AIII)**.

Management of COVID-19

- Recommendations for the triage, management, and treatment of COVID-19 in people with HIV are generally the same as those for the general population **(AIII)**.
- Nonhospitalized people with HIV and mild to moderate COVID-19 may be eligible to receive anti-SARS-CoV-2 therapy (e.g., ritonavir-boosted nirmatrelvir [Paxlovid], remdesivir, molnupiravir). However, in situations where there are logistical or supply constraints for administering these drugs, priority should be given to those with very advanced HIV (e.g., those with CD4 counts <50 cells/mm^3) **(AIII)**. See Prioritization of Anti-SARS-CoV-2 Therapies for the Treatment and Prevention of COVID-19 When There Are Logistical or Supply Constraints for details.
- People with HIV who are taking ritonavir-based or cobicistat-based antiretroviral therapy (ART) can receive ritonavir-boosted nirmatrelvir to treat COVID-19 without altering or interrupting their ART (i.e., they can continue using the ritonavir or cobicistat dose that is associated with their ART in addition to the dose of ritonavir that is used with nirmatrelvir).
- In people with advanced HIV and suspected or documented COVID-19, HIV-associated opportunistic infections should also be considered in the differential diagnosis of febrile illness **(AIII)**.
- When starting treatment for COVID-19 in patients with HIV, clinicians should pay careful attention to potential drug-drug interactions and overlapping toxicities among COVID-19 treatments, antiretroviral (ARV) medications, antimicrobial therapies, and other medications **(AIII)**.
- People with HIV should be offered the opportunity to participate in clinical trials that are evaluating agents for the prevention and treatment of SARS-CoV-2 infection.

Management of HIV

- People with HIV who develop COVID-19, including those who require hospitalization, should continue their ART and opportunistic infection treatment and prophylaxis whenever possible **(AIII)**.
- Clinicians who are treating COVID-19 in people with HIV should consult an HIV specialist before adjusting or switching ARV medications **(AIII)**.

Summary Recommendations, continued
• 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.
Each recommendation in the Guidelines receives 2 ratings that reflect the strength of the recommendation and the quality of the evidence that supports it. See Guidelines Development for more information.

Introduction

Approximately 1.2 million people in the United States are living with HIV. Most of these individuals are in care, and many are on antiretroviral therapy (ART) and have well-controlled disease.[1] Similar to COVID-19, HIV disproportionately affects racial and ethnic minorities and people of lower socioeconomic status in the United States;[2] these demographic groups also appear to have a higher risk of poor outcomes with COVID-19. In the general population, the individuals who are at the highest risk of severe COVID-19 include those aged >60 years; those who are pregnant; those who have received solid organ transplants; and those with comorbidities, such as cancer, obesity, diabetes mellitus, cardiovascular disease, pulmonary disease, a history of smoking, chronic kidney disease, or chronic liver disease.[3] Many people with HIV have 1 or more comorbidities that may put them at increased risk for a more severe course of COVID-19.

Information on SARS-CoV-2/HIV coinfection is evolving rapidly. The sections below outline the current state of knowledge regarding preventing and diagnosing SARS-CoV-2 infection in people with HIV, the treatment and clinical outcomes in people with HIV who develop COVID-19, and the management of HIV during the COVID-19 pandemic. In addition to these Guidelines, the Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents has developed the Guidance for COVID-19 and People With HIV.

Clinical Outcomes of COVID-19 in People With HIV

Data are emerging on the clinical outcomes of COVID-19 in people with HIV. In some of the initial case series of people with COVID-19 in Europe and the United States, no significant differences were observed in the clinical outcomes of COVID-19 between people with HIV and people who did not have HIV.[4-11]

In contrast, more recent reports suggest worse outcomes for patients with HIV and COVID-19, including increased COVID-19 mortality rates in cohort studies in the United States, the United Kingdom, and South Africa.[12-18] HIV was independently associated with an increased risk of severe and critical COVID-19 in a large World Health Organization platform trial that included data from 24 countries.[19] In a multicenter cohort study of 286 patients with HIV and COVID-19 in the United States, lower CD4 T lymphocyte (CD4) cell counts (i.e., <200 cells/mm^3) were associated with a higher risk for the composite endpoint of intensive care unit admission, mechanical ventilation, or death. This increased risk was observed even in patients who had achieved virologic suppression of HIV.[15] In a large observational cohort study of people with HIV and COVID-19 in the United States, those with CD4 counts <350 cells/mm^3 were more likely to be hospitalized, require ventilation, or die. Higher levels of viremia were also associated with worse outcomes.[18] In another study of 175 patients with HIV and COVID-19, a low CD4 count or a low CD4 nadir was associated with poor outcomes.[16] In a cohort study conducted in New York, people with HIV and COVID-19 had higher rates of hospitalization and mortality than people with COVID-19 who did not have HIV.[17]

Prevention of COVID-19 in People With HIV

The COVID-19 Treatment Guidelines Panel (the Panel) recommends using the same approach for advising persons with HIV on the strategies to prevent SARS-CoV-2 infection that is used for people without HIV **(AIII)**. There is currently no clear evidence that any antiretroviral (ARV) medications can prevent SARS-CoV-2 infection.

People with HIV should receive COVID-19 vaccines, regardless of their CD4 count or HIV viral load, because the potential benefits outweigh the potential risks **(AIII)**. People with HIV were included in the clinical trials of the 2 mRNA vaccines and the adenovirus vector vaccine that are currently available through Emergency Use Authorizations (EUAs) and/or approval from the Food and Drug Administration (FDA);[20-22] however, few studies have evaluated the safety and efficacy of these vaccines in people with HIV. Typically, people with HIV who are on ART and who have achieved virologic suppression respond well to licensed vaccines. Preliminary data from studies that used COVID-19 vaccines in people with HIV confirm that people who are on ART and have normal CD4 counts have good immunologic responses to the vaccines.[23-25]

On August 12, 2021, the FDA changed the EUAs for the 2 mRNA vaccines to allow a third dose of an mRNA vaccine to be administered at least 28 days after the second dose to people with advanced or untreated HIV. Advanced HIV is defined as people with CD4 counts <200 cells/mm^3, a history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV. People with HIV should also receive booster doses of the COVID-19 vaccines as recommended by the Advisory Committee on Immunization Practices.

People with advanced or untreated HIV who are not infected or recently exposed to SARS-CoV-2 are eligible to receive the anti-SARS-CoV-2 monoclonal antibodies (mAbs) tixagevimab plus cilgavimab as pre-exposure prophylaxis (PrEP). See Prevention of SARS-CoV-2 Infection for details.

Two anti-SARS-CoV-2 mAb combinations, **bamlanivimab plus etesevimab** and **casirivimab plus imdevimab,** have received FDA EUAs for post-exposure prophylaxis (PEP). However, the Panel **recommends against** their use in patients with COVID-19, including in people with HIV, because the Omicron variant is currently the dominant variant in the United States, and it is not susceptible to these anti-SARS-CoV-2 mAbs **(AIII)**.

Diagnostic and Laboratory Testing for COVID-19 in People With HIV

Diagnosis of COVID-19 in People With HIV

The Panel recommends using the same approach for diagnosing SARS-CoV-2 infection in people with HIV as in those without HIV **(AIII)**. See Testing for SARS-CoV-2 Infection for more information. There is currently no evidence that the performance characteristics of nucleic acid amplification tests (NAATs) and antigen tests differ in people with and without HIV when diagnosing acute SARS-CoV-2 infection. The Panel **recommends against** the use of serologic testing as the sole basis for diagnosis of acute SARS-CoV-2 infection **(AIII)**. However, if diagnostic serologic testing is performed in a patient with HIV, the results should be interpreted with caution because cross-reactivity between antibodies to SARS-CoV-2 and HIV has been reported.[26]

Correlation of CD4 Count in People With HIV and COVID-19

The normal range for CD4 counts in healthy adults is about 500 to 1,600 cells/mm^3. People with HIV who have a CD4 count of ≥500 cells/mm^3 have similar cellular immune function to those without HIV. In people with HIV, a CD4 count <200 cells/mm^3 meets the definition for AIDS. For patients on ART, the hallmark of treatment success is plasma HIV RNA below the level of detection by a polymerase

chain reaction assay. Lymphopenia is a common laboratory finding in patients with COVID-19; in patients with HIV, clinicians should note that CD4 counts obtained during acute COVID-19 may not accurately reflect the patient's HIV disease stage.

There have been some reports of people with advanced HIV who have presented with COVID-19 and another coinfection, including *Pneumocystis jirovecii* pneumonia.[27,28] In patients with advanced HIV who have suspected or laboratory-confirmed SARS-CoV-2 infection, clinicians should consider a broader differential diagnosis for clinical symptoms and consider consulting an HIV specialist **(AIII)**.

Clinical Presentation of COVID-19 in People With HIV

It is currently unknown whether people with HIV have a higher incidence of SARS-CoV-2 infection or a higher rate of progression to symptomatic disease than the general population. Approximately 50% of people with HIV in the United States are aged >50 years,[29] and many have comorbidities that are associated with more severe cases of COVID-19. These comorbidities include hypertension, diabetes mellitus, cardiovascular disease, a history of smoking, chronic lung disease, chronic liver disease, and cancer.[30]

There are a number of case reports and case series that describe the clinical presentation of COVID-19 in people with HIV.[4-11,31,32] These studies indicate that the clinical presentation of COVID-19 is similar in people with and without HIV. Most of the published reports describe populations in which most of the individuals with HIV are on ART and have achieved virologic suppression. Consequently, the current understanding of the impact of COVID-19 in those with advanced HIV who have low CD4 counts or persistent HIV viremia is limited.

Management of COVID-19 in People With HIV

Recommendations for the triage and management of COVID-19 in people with HIV are the same as those for the general population **(AIII)**.

The treatment of COVID-19 in persons with HIV is the same as for those without HIV **(AIII)**. Nonhospitalized people with HIV and mild to moderate COVID-19 may be eligible to receive the therapies that are currently recommended for treatment (see Therapeutic Management of Nonhospitalized Adults With COVID-19). However, in situations where there are logistical or supply constraints for administering these therapies, priority should be given to those with advanced HIV **(AIII)**.

When starting treatment for COVID-19 in patients with HIV, clinicians should pay careful attention to potential drug-drug interactions and overlapping toxicities among COVID-19 treatments, ARV medications, antimicrobial therapies, and other medications **(AIII)**. Therapeutic options for nonhospitalized patients with HIV include ritonavir-boosted nirmatrelvir (Paxlovid), intravenous remdesivir, and molnupiravir (see Therapeutic Management of Nonhospitalized Adults With COVID-19). Drug-drug interactions are a special concern with ritonavir-boosted nirmatrelvir (see Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir [Paxlovid] and Concomitant Medications). People with HIV who are taking ritonavir-based or cobicistat-based ART can receive the 5-day course of ritonavir-boosted nirmatrelvir to treat COVID-19 without altering or interrupting their ART (i.e., they can continue using the ritonavir or cobicistat dose that is associated with their ART in addition to the dose of ritonavir that is used with nirmatrelvir). Before prescribing ritonavir-boosted nirmatrelvir for a patient who is not already on a ritonavir-based or cobicistat-based regimen, clinicians should carefully review the patient's concomitant medications, including over-the-counter medicines and herbal supplements, and evaluate the potential for drug-drug interactions. Clinicians should utilize resources such as the EUA fact sheet for ritonavir-boosted nirmatrelvir and the Liverpool COVID-19

Drug Interactions website for additional guidance on identifying and managing drug-drug interactions.

In hospitalized patients, the appropriate treatment strategy depends on disease severity (see Therapeutic Management of Hospitalized Adults With COVID-19). Both tocilizumab and dexamethasone, which are recommended for some patients with severe or critical COVID-19, are immunosuppressive agents. The safety of using these drugs in immunocompromised patients, including those with advanced HIV, has not been studied. Therefore, patients with advanced HIV who are receiving these drugs should be closely monitored for secondary infections. Dexamethasone is a dose-dependent inducer of cytochrome P450 3A4 and could potentially lower the levels of certain coadministered ARV drugs. More than a single dose of dexamethasone **is not recommended** for patients who are receiving rilpivirine as part of their ARV regimen. Clinicians should consult an HIV specialist before administering dexamethasone to these patients. It is currently unknown whether administering ≤10 days of dexamethasone impacts the clinical efficacy of other ARV drugs. Patients with HIV who are receiving dexamethasone as treatment for COVID-19 should follow up with their HIV providers to assess their virologic response.

Although some ARV drugs were studied for the prevention and treatment of COVID-19, no agents have been shown to be effective.

People with HIV should be offered the opportunity to participate in clinical trials of vaccines and potential treatments for COVID-19. A variety of immunomodulatory therapies are prescribed empirically or administered as part of a clinical trial to treat severe COVID-19. The data on whether these medications are safe to use in patients with HIV are lacking. If a medication has been shown to reduce the mortality of patients with COVID-19 in the general population, it should also be used to treat COVID-19 in patients with HIV, unless data indicate that the medication is not safe or effective in this population.

Managing HIV in People With COVID-19

Whenever possible, ART and opportunistic infection prophylaxis should be continued in a patient with HIV who develops COVID-19, including in those who require hospitalization **(AIII)**. Treatment interruption may lead to rebound viremia, and, in some cases, the emergence of drug resistance. If the appropriate ARV drugs are not on the hospital's formulary, administer medications from the patient's home supplies, if available.

Clinicians who are treating COVID-19 in people with HIV should consult an HIV specialist before adjusting or switching a patient's ARV medications. An ARV regimen should not be switched or adjusted (i.e., by adding ARV drugs to the regimen) for the purpose of preventing or treating SARS-CoV-2 infection **(AIII)**. Many drugs, including some ARV agents (e.g., lopinavir/ritonavir, boosted darunavir, tenofovir disoproxil fumarate/emtricitabine), have been or are being evaluated in clinical trials or are prescribed off-label to treat or prevent SARS-CoV-2 infection. To date, lopinavir/ritonavir and darunavir/cobicistat have not been found to be effective.[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 Clinician Consultation Center, Monday through Friday, 9 am to 8 pm EST.

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

Last Updated: December 1, 2022

Name	Affiliation
Co-Chairs	
Roy M. Gulick, MD, MPH	Weill Cornell Medicine, New York, NY
H. Clifford Lane, MD	National Institutes of Health, Bethesda, MD
Henry Masur, MD	National Institutes of Health, Bethesda, MD
Executive Secretary	
Alice K. Pau, PharmD	National Institutes of Health, Bethesda, MD
Members	
Judith Aberg, MD	Icahn School of Medicine at Mount Sinai, New York, NY
Adaora Adimora, MD, MPH	University of North Carolina School of Medicine, Chapel Hill, NC
Jason Baker, MD, MS	Hennepin Healthcare/University of Minnesota, Minneapolis, MN
Lisa Baumann Kreuziger, MD, MS	Versiti/Medical College of Wisconsin, Milwaukee, WI
Roger Bedimo, MD, MS	University of Texas Southwestern/Veterans Affairs North Texas Health Care System, Dallas, TX
Pamela S. Belperio, PharmD	Department of Veterans Affairs, Los Angeles, CA
Anoopindar Bhalla, MD	Children's Hospital Los Angeles/University of Southern California, Los Angeles, CA
Stephen V. Cantrill, MD	Denver Health, Denver, CO
Kathleen Chiotos, MD, MSCE	Children's Hospital of Philadelphia/University of Pennsylvania, Philadelphia, PA
Craig Coopersmith, MD	Emory University School of Medicine, Atlanta, GA
Eric Daar, MD	Harbor-UCLA Medical Center, Torrance, CA
Amy L. Dzierba, PharmD	New York-Presbyterian Hospital, New York, NY
Gregory Eschenauer, PharmD	University of Michigan, Ann Arbor, MI
Laura Evans, MD, MSc	University of Washington, Seattle, WA
John J. Gallagher, DNP, RN	University of Pittsburgh Medical Center, Pittsburgh, PA
Rajesh Gandhi, MD	Massachusetts General Hospital/Harvard Medical School, Boston, MA
David V. Glidden, PhD	University of California San Francisco, San Francisco, CA
Birgit Grund, PhD	University of Minnesota, Minneapolis, MN
Erica J. Hardy, MD, MMSc	Warren Alpert Medical School of Brown University, Providence, RI
Lauren Henderson, MD, MMSc	Boston Children's Hospital/Harvard Medical School, Boston, MA
Carl Hinkson, MSRC	Providence Health & Services, Everett, WA
Brenna L. Hughes, MD, MSc	Duke University School of Medicine, Durham, NC
Steven Johnson, MD	University of Colorado School of Medicine, Aurora, CO
Marla J. Keller, MD	Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY
Arthur Kim, MD	Massachusetts General Hospital/Harvard Medical School, Boston, MA
Jeffrey L. Lennox, MD	Emory University School of Medicine, Atlanta, GA
Mitchell M. Levy, MD	Warren Alpert Medical School of Brown University, Providence, RI
Jonathan Li, MD, MMSc	Brigham and Women's Hospital/Harvard Medical School, Boston, MA
Christine MacBrayne, PharmD, MSCS	Children's Hospital Colorado, Aurora, CO
Gregory Martin, MD, MSc	Emory University School of Medicine, Atlanta, GA
Susanna Naggie, MD, MHS	Duke University School of Medicine, Durham, NC
Andrew T. Pavia, MD	University of Utah School of Medicine, Salt Lake City, UT

Name	Affiliation
Members, continued	
Grant Schulert, MD, PhD	Cincinnati Children's Hospital Medical Center/University of Cincinnati College of Medicine, Cincinnati, OH
Nitin Seam, MD	National Institutes of Health, Bethesda, MD
Steven Q. Simpson, MD	University of Kansas Medical Center, Kansas City, KS
Renee Stapleton, MD, PhD	University of Vermont Larner College of Medicine, Burlington, VT
Susan Swindells, MBBS	University of Nebraska Medical Center, Omaha, NE
Pablo Tebas, MD	University of Pennsylvania, Philadelphia, PA
Phyllis Tien, MD, MSc	University of California, San Francisco/San Francisco VA Healthcare System, San Francisco, CA
Alpana A. Waghmare, MD	Seattle Children's Hospital, Seattle, WA
Jinoos Yazdany, MD, MPH	University of California, San Francisco, San Francisco, CA
Community Members	
Danielle M. Campbell, MPH	University of California, Los Angeles, Los Angeles, CA
Carly Harrison	LupusChat, New York, NY
Pharmacology Consultants	
Sarita Boyd, PharmD	Food and Drug Administration, Silver Spring, MD
Jomy George, PharmD	National Institutes of Health, Bethesda, MD
Kimberly Scarsi, PharmD	University of Nebraska Medical Center, Omaha, NE
Ex Officio Members, U.S. Government Representatives	
Timothy Burgess, MD	Department of Defense, Bethesda, MD
Demetre Daskalakis, MD, MPH	Centers for Disease Control and Prevention, Atlanta, GA
Derek Eisnor, MD	Biomedical Advanced Research and Development Authority, Washington, DC
Joseph Francis, MD, MPH	Department of Veterans Affairs, Washington, DC
Virginia Sheikh, MD, MHS	Food and Drug Administration, Silver Spring, MD
Timothy M. Uyeki, MD, MPH	Centers for Disease Control and Prevention, Atlanta, GA
U.S. Government Support Team	
John T. Brooks, MD	Centers for Disease Control and Prevention, Atlanta, GA
Richard T. Davey, Jr., MD	National Institutes of Health, Bethesda, MD
Laurie K. Doepel, BA	National Institutes of Health, Bethesda, MD
Alison Han, MD (Co-Team Coordinator)	National Institutes of Health, Bethesda, MD
Elizabeth S. Higgs, MD, DTM&H, MIA	National Institutes of Health, Bethesda, MD
Martha C. Nason, PhD (Biostatistics Support)	National Institutes of Health, Bethesda, MD
Michael Proschan, PhD (Biostatistics Support)	National Institutes of Health, Bethesda, MD
Renee Ridzon, MD	National Institutes of Health, Bethesda, MD
Kanal Singh, MD, MPH (Co-Team Coordinator)	National Institutes of Health, Bethesda, MD
Assistant Executive Secretaries	
Page Crew, PharmD, MPH	National Institutes of Health, Bethesda, MD
Safia Kuriakose, PharmD	Frederick National Laboratory for Cancer Research, in support of NIAID, Frederick, MD
Andrea M. Lerner, MD, MS	National Institutes of Health, Bethesda, MD

Appendix A, Table 2. COVID-19 Treatment Guidelines Panel Financial Disclosure for Companies Related to COVID-19 Treatment or Diagnostics

Last Updated: December 1, 2022

Reporting Period: April 1, 2021, to March 31, 2022

Panel Member	Financial Disclosure	
	Company	Relationship
Judith Aberg, MD	Atea Pharmaceuticals	Research support
	Emergent BioSolutions	Research support
	Gilead Sciences	Research support
	GSK	Advisory board, research support
	GSK/ViiV Healthcare	Advisory board, research support
	Janssen	Research support
	Merck & Co.	Advisory board, research support
	Pfizer	Research support
	Regeneron	Research support
Adaora Adimora, MD, MPH	Gilead Sciences	Research support, consultant
	Merck & Co.	Advisory board, research support
Jason Baker, MD, MS	Humanigen	Research support
Lisa Baumann Kreuziger, MD, MS	3M	Stockholder, spouse is an employee
	Versiti	Employee
Roger Bedimo, MD, MS	Gilead Sciences	Advisory board
	GSK/ViiV Healthcare	Advisory board
	Janssen	Advisory board
	Merck & Co.	Advisory board, research support
Pamela S. Belperio, PharmD	None	N/A
Anoopindar Bhalla, MD	None	N/A
John T. Brooks, MD	None	N/A
Timothy Burgess, MD	AstraZeneca	Research support
Danielle M. Campbell, MPH	Gilead Sciences	Advisory board
	GSK/ViiV Healthcare	Attendee at the community stakeholder meeting
Stephen V. Cantrill, MD	None	N/A
Kathleen Chiotos, MD, MSCE	None	N/A
Craig Coopersmith, MD	None	N/A
Page Crew, PharmD, MPH	None	N/A
Eric Daar, MD	Gilead Sciences	Consultant, research support
	GSK/ViiV Healthcare	Consultant, research support
	Merck & Co.	Consultant, research support
Demetre Daskalakis, MD, MPH	None	N/A
Richard T. Davey, Jr., MD	None	N/A

Panel Member	Financial Disclosure	
	Company	Relationship
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
Laura Evans, MD, MSc	None	N/A
Joseph Francis, MD, MPH	None	N/A
John J. Gallagher, DNP, RN	None	N/A
Rajesh Gandhi, MD	None	N/A
David V. Glidden, PhD	None	N/A
Birgit Grund, PhD	None	N/A
Roy M. Gulick, MD, MPH	None	N/A
Alison Han, MD	None	N/A
Erica J. Hardy, MD, MMSc	None	N/A
Carly Harrison	AstraZeneca	Advisory board, consultant
	Aurinia Pharmaceuticals	Advisory board, stockholder
	UCB	Advisory board, consultant
Lauren Henderson, MD, MMSc	Adaptive Biotechnologies	Consultant
	Bristol Myers Squibb	Research support
	Pfizer	External panel for grant reviews
	Sobi	Advisory board, consultant, research support
	Skygenic	Consultant, spouse is an employee
Elizabeth S. Higgs, MD, DTM&H, MIA	None	N/A
Carl Hinkson, MSRC	None	N/A
Brenna L. Hughes, MD, MSc	None	N/A
Steven Johnson, MD	GSK/ViiV Healthcare	Advisory board
Marla J. Keller, MD	None	N/A
Arthur Kim, MD	Kintor Pharmaceutical	Data and safety monitoring board chair/member
Safia Kuriakose, PharmD	None	N/A
H. Clifford Lane, MD	None	N/A
Jeffrey L. Lennox, MD	None	N/A
Andrea M. Lerner, MD, MS	None	N/A
Mitchell M. Levy, MD	None	N/A
Jonathan Li, MD, MMSc	None	N/A
Christine MacBrayne, PharmD, MSCS	None	N/A
Gregory Martin, MD, MSc	Genentech	Data and safety monitoring board chair/member
	Grifols	Research grants review panel
Henry Masur, MD	None	N/A

Panel Member	Financial Disclosure	
	Company	Relationship
Susanna Naggie, MD, MHS	AbbVie	Research support, funding via NIH-supported trial
	Bristol Myers Squibb	Event adjudication committee
	FHI 360	Event adjudication committee
	Gilead Sciences	Research support
	Pardes Biosciences	Consultant
	Silverback Therapeutics	Consultant
	Vir Biotechnology	Advisory board, stockholder, stock options
Martha C. Nason, PhD	None	N/A
Alice K. Pau, PharmD	None	N/A
Andrew T. Pavia, MD	GSK	Advisory board
Michael Proschan, PhD	None	N/A
Renee Ridzon, MD	None	N/A
Grant Schulert, MD, PhD	Novartis	Honoraria
Nitin Seam, MD	None	N/A
Virginia Sheikh, MD, MHS	None	N/A
Steven Q. Simpson, MD	None	N/A
Kanal Singh, MD, MPH	None	N/A
Renee Stapleton, MD, PhD	Altimmune	Data and safety monitoring board chair
	CSL Behring	Consultant
Susan Swindells, MBBS	GSK/ViiV Healthcare	Research support
Pablo Tebas, MD	Gilead Sciences	Consultant
	GSK/ViiV Healthcare	Consultant
	Merck & Co.	Consultant
Phyllis Tien, MD, MSc	Eli Lilly	Research support
	Gilead Sciences	Research support
	Merck & Co.	Research support
Timothy M. Uyeki, MD, MPH	None	N/A
Alpana A. Waghmare, MD	AlloVir	Research support
	Ansun Biopharma	Research support
	Deverra Therapeutics	Data and safety monitoring board member
	KYORIN Pharmaceutical Co.	Advisory board
	Pfizer	Research support
	Vir Biotechnology	Research support
Jinoos Yazdany, MD, MPH	AstraZeneca	Consulting and research support related to lupus
	Aurinia	Consulting related to lupus drug
	Bristol Myers Squibb	Research support
	Pfizer	Consultant, lecture presenter