Coronavirus Disease 2019 (COVID-19) Treatment Guidelines

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

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What's New in the Guidelines

Last Updated: April 1, 2022

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

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

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

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

April 1, 2022

Therapeutic Management of Nonhospitalized Adults With COVID-19

The Omicron BA.2 subvariant is rapidly becoming the dominant subvariant in many regions of the United States. Previously, the Panel recommended sotrovimab, an anti-SARS-CoV-2 monoclonal antibody (mAb), as 1 of the preferred therapies for the treatment of nonhospitalized patients with mild to moderate COVID-19 who are at high risk of progressing to severe disease. Even though sotrovimab is active against the Omicron BA.1 and BA.1.1 subvariants, it has substantially decreased in vitro activity against the BA.2 subvariant. The Food and Drug Administration (FDA) recently updated the Emergency Use Authorization (EUA) for sotrovimab to note that it is not authorized for use in geographic regions where infection is likely to have been caused by nonsusceptible SARS-CoV-2 variants, and distribution of sotrovimab has been paused in these regions.

As a result of these recent changes and the increasing prevalence of the BA.2 subvariant across all regions, the Panel no longer recommends sotrovimab as a preferred therapy for nonhospitalized patients with mild to moderate COVID-19 who are at high risk of progressing to severe disease.

The Panel's revised recommendations are outlined below.

Preferred Therapies

Listed in order of preference:

- **Ritonavir-boosted nirmatrelvir (Paxlovid) (AIIa)**
- **Remdesivir (BIIa)**

Alternative Therapies

For use ONLY when neither of the preferred therapies are available, feasible to use, or clinically appropriate. Listed in alphabetical order:

- **Bebtelovimab (CIII)**
- **Molnupiravir (CIIa)**

For use **ONLY** in regions where the Omicron BA.2 subvariant is not the dominant subvariant and in

situations where none of the preferred or alternative options are available, feasible to use, or clinically appropriate:

- **Sotrovimab (CIII)**

The text and Figure 1 in Therapeutic Management of Nonhospitalized Adults With COVID-19 have been updated to include the rationale that supports these new recommendations. This section also now incorporates information from the Panel's previously published statement on the role of bebtelovimab in the treatment of these patients.

Table 3c. Characteristics of SARS-CoV-2 Antibody-Based Products

This section includes new information on bebtelovimab, distribution information for sotrovimab, and updated dosing information for tixagevimab plus cilgavimab (Evusheld).

March 24, 2022

Testing for SARS-CoV-2 Infection

The FDA has issued more than 80 EUAs for SARS-CoV-2 serologic or antibody tests since the start of the pandemic. These tests are authorized for detecting SARS-CoV-2 antibodies, but their ability to predict protective immunity has not been validated.

The Panel previously recommended against the use of serologic testing to determine whether a person is immune to SARS-CoV-2 infection. Recently, there has been an increasing interest in using serologic testing to guide decisions about administering additional vaccines or anti-SARS-CoV-2 therapy to certain individuals. Based on the available information, the Panel has determined that there is insufficient evidence to recommend either for or against the use of SARS-CoV-2 serologic testing to assess for immunity or to guide clinical decisions on the use of COVID-19 vaccines or anti-SARS-CoV-2 mAbs in certain people.

Prevention of SARS-CoV-2 Infection

In December 2021, the FDA issued an EUA to allow the anti-SARS-CoV-2 mAbs tixagevimab 150 mg plus cilgavimab 150 mg (Evusheld) to be used as pre-exposure prophylaxis (PrEP) in certain individuals. Recent in vitro data has shown that the BA.1 and BA.1.1 subvariants of the Omicron variant have a decreased susceptibility to tixagevimab and cilgavimab. As a result, on February 24, 2022, the FDA revised the EUA to increase the dose to tixagevimab 300 mg plus cilgavimab 300 mg for those who are receiving these anti-SARS-CoV-2 mAbs for first time. For those who received the originally authorized dose, the revised EUA recommends administering an additional dose of tixagevimab 150 mg plus cilgavimab 150 mg as soon as possible. These new recommendations are based on pharmacokinetic/pharmacodynamic modeling projections. To date, there are no clinical data that support the efficacy of these new doses.

In this revised section, the Panel provides new recommendations on the dosing of tixagevimab and cilgavimab and discusses some important limitations to the current recommendations.

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

This new section incorporates information from the Panel's previously published statement on patient prioritization for outpatient therapies, which was released in December 2021.

Granulocyte-Macrophage Colony-Stimulating Factor Inhibitors

The text and clinical data table for this section have been updated to include recently published data.

Introduction

Last Updated: July 8, 2021

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

Panel Composition

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

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

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

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

Development of the Guidelines

Each section of the Guidelines is developed by a working group of Panel members with expertise in the

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

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

Method of Synthesizing Data and Formulating Recommendations

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

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

Table 1. Recommendation Rating Scheme

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

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

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

- **The Panel recommends using [blank] for the treatment of COVID-19 (rating).** Recommendations in this category are based on evidence from clinical trials or large cohort studies that demonstrate the clinical or virologic efficacy of a therapy in patients with COVID-19, with the potential benefits outweighing the potential risks.
- **There is insufficient evidence for the Panel to recommend either for or against the use of [blank] for the treatment of COVID-19 (no rating).** This statement is used when the collective results from clinical trials and/or observational cohorts do not provide the evidence needed to support a recommendation due to too few or conflicting data.
- **The Panel recommends against the use of [blank] for the treatment of COVID-19, except in a clinical trial (rating).** This recommendation is used for an intervention that has not clearly

demonstrated efficacy in the treatment of COVID-19 and/or has potential safety concerns. More clinical trials are needed to further define the role of the intervention.

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

Evolving Knowledge on Treatment for COVID-19

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

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

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

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

Overview of COVID-19

Last Updated: February 24, 2022

Epidemiology

The COVID-19 pandemic has exploded since cases were first reported in China in December 2019. As of February 22, 2022, more than 426 million cases of COVID-19—caused by SARS-CoV-2 infection—have been reported globally, including more than 5.8 million deaths.[1]

Individuals of all ages are at risk for SARS-CoV-2 infection and severe disease. However, the probability of serious COVID-19 disease is higher in people aged ≥60 years, those living in a nursing home or long-term care facility, and those with chronic medical conditions. In an analysis of more than 1.3 million laboratory-confirmed cases of COVID-19 that were reported in the United States between January and May 2020, 14% of patients required hospitalization, 2% were admitted to the intensive care unit, and 5% died.[2] The percentage of patients who died was 12 times higher among those with reported medical conditions (19.5%) than among those without medical conditions (1.6%), and the percentage of those who were hospitalized was 6 times higher among those with reported medical conditions (45.4%) than among those without medical conditions (7.6%). The mortality rate was highest in those aged >70 years, regardless of the presence of chronic medical conditions. Among those with available data on health conditions, 32% had cardiovascular disease, 30% had diabetes, and 18% had chronic lung disease. Other conditions that may lead to a high risk for severe COVID-19 include cancer, kidney disease, liver disease (especially in patients with cirrhosis), obesity, sickle cell disease, and other immunocompromising conditions. Transplant recipients and pregnant people are also at a higher risk of severe COVID-19.[3-10]

Data from the United States suggest that racial and ethnic minorities experience higher rates of COVID-19 and subsequent hospitalization and death.[11-15] However, surveillance data that include race and ethnicity are not available for most reported cases of COVID-19 in the United States.[4,16] Factors that contribute to the increased burden of COVID-19 in these populations may include over-representation in work environments that confer higher risks of exposure to COVID-19, economic inequality (which limits people's ability to protect themselves against COVID-19 exposure), neighborhood disadvantage,[17] and a lack of access to health care.[16] Structural inequalities in society contribute to health disparities for racial and ethnic minority groups, including higher rates of comorbid conditions (e.g., cardiac disease, diabetes, hypertension, obesity, pulmonary diseases), which further increases the risk of developing severe COVID-19.[15]

SARS-CoV-2 Variants

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

Since December 2020, several variants have been identified that have now been assigned Greek letter designations by the World Health Organization (WHO). SARS-CoV-2 variants are designated as variants of concern (VOC) if they display certain characteristics, such as increased transmissibility or virulence. In addition, vaccines and/or therapeutics may have decreased effectiveness against VOC, and the mutations found in these variants may interfere with diagnostic test targets. The designation variant

of interest (VOI) is used for important variants that have not yet been fully characterized; however, the designations and definitions for these variants differ between organizations.[22,23] In September 2021, the Centers for Disease Control and Prevention (CDC) added a new designation for variants: variants being monitored (VBM). This refers to variants for which the data indicate a potential or clear impact on approved or authorized medical countermeasures, or variants that have been associated with more severe disease or increased transmission rates; however, these variants are either no longer detected or are circulating at very low levels in the United States. As such, these variants do not pose a significant and imminent risk to public health in the United States.

The B.1.1.529 (Omicron) variant was designated a VOC in November 2021 and rapidly became the dominant variant across the globe. The Omicron VOC is more transmissible than other variants and is not susceptible to some of the anti-SARS-CoV-2 mAbs that have been developed for treatment and prevention.[20,21,24] The Omicron VOC replaced the B.1.617.2 (Delta) variant, which was first identified in India and became the dominant variant in the United States after the summer of 2021.[25]

Earlier variants included the B.1.1.7 (Alpha) variant, which was first seen in the United Kingdom and has been shown to be highly infectious and possibly more virulent than previously reported variants.[26-28] The B.1.351 (Beta) variant was originally identified in South Africa, and the P.1 (Gamma) variant was identified in Manaus, Brazil. Both of these demonstrated reduced susceptibility to select anti-SARS-CoV-2 mAbs used for treatment and prevention. While the Alpha, Beta, and Gamma variants were previously designated as VOC, they have largely disappeared worldwide. For a detailed discussion on the susceptibility of certain VOC, VOI, and VBM to available anti-SARS-CoV-2 mAbs, please see Anti-SARS-CoV-2 Monoclonal Antibodies.

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

Clinical Presentation

The estimated incubation period for COVID-19 is up to 14 days from the time of exposure, with a median incubation period of 4 to 5 days.[6,29,30] The spectrum of illness can range from asymptomatic infection to severe pneumonia with acute respiratory distress syndrome and death. Among 72,314 people with COVID-19 in China, 81% of cases were reported to be mild (defined in this study as no pneumonia or mild pneumonia), 14% were severe (defined as dyspnea, respiratory frequency ≥30 breaths/min, oxygen saturation [SpO_2] ≤93%, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen [PaO_2/FiO_2] <300 mm Hg, and/or lung infiltrates >50% within 24 to 48 hours), and 5% were critical (defined as respiratory failure, septic shock, and/or multiorgan dysfunction or failure).[31] In a report on more than 370,000 confirmed COVID-19 cases with reported symptoms in the United States, 70% of patients experienced fever, cough, or shortness of breath, 36% had muscle aches, and 34% reported headaches.[2] Other reported symptoms have included, but are not limited to, diarrhea, dizziness, rhinorrhea, anosmia, dysgeusia, sore throat, abdominal pain, anorexia, and vomiting.

The abnormalities seen in chest X-rays of patients with COVID-19 vary, but bilateral multifocal opacities are the most common. The abnormalities seen in computed tomography of the chest also vary, but the most common are bilateral peripheral ground-glass opacities, with areas of consolidation

developing later in the clinical course of COVID-19.[32] Imaging may be normal early in infection and can be abnormal in the absence of symptoms.[32]

Common laboratory findings in patients with COVID-19 include leukopenia and lymphopenia. Other laboratory abnormalities have included elevated levels of aminotransferase, C-reactive protein, D-dimer, ferritin, and lactate dehydrogenase.

Although COVID-19 is primarily a pulmonary disease, emerging data suggest that it also leads to cardiac,[33,34] dermatologic,[35] hematologic,[36] hepatic,[37] neurologic,[38,39] renal,[40,41] and other complications. Thromboembolic events also occur in patients with COVID-19, with the highest risk occurring in critically ill patients.[42]

The long-term sequelae of COVID-19 survivors are currently unknown. Persistent symptoms after recovery from acute COVID-19 have been described (see Clinical Spectrum of SARS-CoV-2 Infection). Lastly, SARS-CoV-2 infection has been associated with a potentially severe inflammatory syndrome in children (multisystem inflammatory syndrome in children, or MIS-C).[43,44] Please see Special Considerations in Children for more information.

References

1. Johns Hopkins. COVID-19 Dashboard by the Center for Science and Engineering. 2021. Available at: https://coronavirus.jhu.edu/map.html. Accessed February 15, 2022.
2. Stokes EK, Zambrano LD, Anderson KN, et al. Coronavirus disease 2019 case surveillance - United States, January 22-May 30, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(24):759-765. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32555134.
3. Cai Q, Chen F, Wang T, et al. Obesity and COVID-19 severity in a designated hospital in Shenzhen, China. *Diabetes Care*. 2020;43(7):1392-1398. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32409502.
4. Centers for Disease Control and Prevention. United States COVID-19 cases, seaths, and laboratory testing (NAATs) by state, territory, and jurisdiction. 2022. Available at: https://covid.cdc.gov/covid-data-tracker/?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fcases-updates%2Fcases-in-us.html#cases_casesper100klast7days. Accessed February 15, 2022.
5. Garg S, Kim L, Whitaker M, et al. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019 - COVID-NET, 14 States, March 1-30, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(15):458-464. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32298251.
6. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382(18):1708-1720. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32109013.
7. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. 2020;180(7):934-943. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32167524.
8. Palaiodimos L, Kokkinidis DG, Li W, et al. Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx, New York. *Metabolism*. 2020;108:154262. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32422233.
9. Zambrano LD, Ellington S, Strid P, et al. Update: characteristics of symptomatic women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status - United States, January 22-October 3, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(44):1641-1647. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33151921.
10. Centers for Disease Control and Prevention. COVID-19: people with certain medical conditions. 2021. Available at: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Accessed December 27, 2021.

11. Azar KMJ, Shen Z, Romanelli RJ, et al. Disparities in outcomes among COVID-19 patients in a large health care system in California. *Health Aff (Millwood)*. 2020;39(7):1253-1262. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32437224.

12. Gold JAW, Wong KK, Szablewski CM, et al. Characteristics and Clinical Outcomes of Adult Patients Hospitalized with COVID-19 - Georgia, March 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(18):545-550. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32379729.

13. Gross CP, Essien UR, Pasha S, et al. Racial and ethnic disparities in population-level COVID-19 mortality. *J Gen Intern Med*. 2020;35(10):3097-3099. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32754782.

14. Nayak A, Islam SJ, Mehta A, et al. Impact of social vulnerability on COVID-19 incidence and outcomes in the United States. *medRxiv*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32511437.

15. Price-Haywood EG, Burton J, Fort D, Seoane L. Hospitalization and mortality among black patients and white patients with COVID-19. *N Engl J Med*. 2020;382(26):2534-2543. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32459916.

16. Centers for Disease Control and Prevention. Health equity considerations & racial & ethnic minority groups. 2022. Available at: https://www.cdc.gov/coronavirus/2019-ncov/community/health-equity/race-ethnicity.html. Accessed February 15, 2022.

17. Kind AJH, Buckingham WR. Making neighborhood-disadvantage metrics accessible - the neighborhood atlas. *N Engl J Med*. 2018;378(26):2456-2458. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29949490.

18. Walensky RP, Walke HT, Fauci AS. SARS-CoV-2 variants of concern in the United States-challenges and opportunities. *JAMA*. 2021;325(11):1037-1038. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33595644.

19. Wang P, Nair MS, Liu L, et al. Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7. *Nature*. 2021;593(7857):130-135. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33684923.

20. Cameroni E, Bowen JE, Rosen LE, et al. Broadly neutralizing antibodies overcome SARS-CoV-2 Omicron antigenic shift. *Nature*. 2021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35016195.

21. Liu L, Iketani S, Guo Y, et al. Striking antibody evasion manifested by the Omicron variant of SARS-CoV-2. *Nature*. 2021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35016198.

22. World Health Organization. Tracking SARS-CoV-2 variants. 2022. Available at: https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/. Accessed February 15, 2022.

23. Centers for Disease Control and Prevention. SARS-CoV-2 variant classifications and definitions. 2021. Available at: https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-classifications.html. Accessed January 24, 2022.

24. Centers for Disease Control and Prevention. Omicron variant: what you need to know. 2022. Available at: https://www.cdc.gov/coronavirus/2019-ncov/variants/omicron-variant.html. Accessed February 15, 2022.

25. Abrams JY, Oster ME, Godfred-Cato SE, et al. Factors linked to severe outcomes in multisystem inflammatory syndrome in children (MIS-C) in the USA: a retrospective surveillance study. *Lancet Child Adolesc Health*. 2021;5(5):323-331. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33711293.

26. Leung K, Shum MH, Leung GM, Lam TT, Wu JT. Early transmissibility assessment of the N501Y mutant strains of SARS-CoV-2 in the United Kingdom, October to November 2020. *Euro Surveill*. 2021;26(1). Available at: https://www.ncbi.nlm.nih.gov/pubmed/33413740.

27. Davies NG, Barnard RC, Jarvis CI, et al. Report: continued spread of VOC 202012/01 in England. 2020. Available at: https://cmmid.github.io/topics/covid19/reports/uk-novel-variant/2020_12_31_Transmissibility_and_severity_of_VOC_202012_01_in_England_update_1.pdf. Accessed.

28. Murugan NA, Javali PS, Pandian CJ, et al. Computational investigation of increased virulence and pathogenesis of SARS-CoV-2 lineage B.1.1.7. *bioRxiv*. 2021;Preprint. Available at: https://www.biorxiv.org/content/10.1101/2021.01.25.428190v1.

29. Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med*. 2020;382(13):1199-1207. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31995857.

30. Lauer SA, Grantz KH, Bi Q, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. *Ann Intern Med*. 2020;172(9):577-582. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32150748.

31. Wu Z, McGoogan JM. Characteristics of and important lessons From the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72,314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323(13):1239-1242. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32091533.

32. Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Lancet Infect Dis*. 2020;20(4):425-434. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32105637.

33. Liu PP, Blet A, Smyth D, Li H. The science underlying COVID-19: implications for the cardiovascular system. *Circulation*. 2020;142(1):68-78. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32293910.

34. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential effects of coronaviruses on the cardiovascular system: a review. *JAMA Cardiol*. 2020;5(7):831-840. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32219363.

35. Sachdeva M, Gianotti R, Shah M, et al. Cutaneous manifestations of COVID-19: report of three cases and a review of literature. *J Dermatol Sci*. 2020;98(2):75-81. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32381430.

36. Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. *Clin Chem Lab Med*. 2020;58(7):1021-1028. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32286245.

37. Agarwal A, Chen A, Ravindran N, To C, Thuluvath PJ. Gastrointestinal and liver manifestations of COVID-19. *J Clin Exp Hepatol*. 2020;10(3):263-265. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32405183.

38. Whittaker A, Anson M, Harky A. Neurological manifestations of COVID-19: a systematic review and current update. *Acta Neurol Scand*. 2020;142(1):14-22. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32412088.

39. Paniz-Mondolfi A, Bryce C, Grimes Z, et al. Central nervous system involvement by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). *J Med Virol*. 2020;92(7):699-702. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32314810.

40. Pei G, Zhang Z, Peng J, et al. Renal involvement and early prognosis in patients with COVID-19 pneumonia. *J Am Soc Nephrol*. 2020;31(6):1157-1165. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32345702.

41. Su H, Yang M, Wan C, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. *Kidney Int*. 2020;98(1):219-227. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32327202.

42. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. *J Am Coll Cardiol*. 2020;75(23):2950-2973. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32311448.

43. Chiotos K, Bassiri H, Behrens EM, et al. Multisystem inflammatory syndrome in children during the coronavirus 2019 pandemic: a case series. *J Pediatric Infect Dis Soc*. 2020;9(3):393-398. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32463092.

44. Belhadjer Z, Meot M, Bajolle F, et al. Acute heart failure in multisystem inflammatory syndrome in children in the context of global SARS-CoV-2 pandemic. *Circulation*. 2020;142(5):429-436. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32418446.

Testing for SARS-CoV-2 Infection

Last Updated: March 24, 2022

Summary Recommendations

• The COVID-19 Treatment Guidelines Panel (the Panel) recommends using a nucleic acid amplification test (NAAT) with a sample collected from the upper respiratory tract (i.e., nasopharyngeal, nasal mid-turbinate, anterior nasal, or oropharyngeal) to diagnose acute infection of SARS-CoV-2; if it is not practical to use a NAAT or if NAATs are not available, an antigen test may be used **(AIII)**.
• For intubated and mechanically ventilated adults who are suspected to have COVID-19 but who do not have a confirmed diagnosis:
  • The Panel recommends obtaining lower respiratory tract samples to establish a diagnosis of COVID-19 if an initial upper respiratory tract sample is negative **(BII)**.
  • The Panel recommends obtaining endotracheal aspirates over bronchial wash or bronchoalveolar lavage samples when collecting lower respiratory tract samples to establish a diagnosis of COVID-19 **(BII)**.
• A NAAT should not be repeated in an asymptomatic person (with the exception of health care workers) within 90 days of a previous SARS-CoV-2 infection, even if the person has had a significant exposure to SARS-CoV-2 **(AIII)**.
• SARS-CoV-2 reinfection has been reported in people after an initial diagnosis of the infection; therefore, clinicians should consider using a NAAT for those who have recovered from a previous infection and who present with symptoms that are compatible with SARS-CoV-2 infection if there is no alternative diagnosis **(BIII)**.
• The Panel **recommends against** the use of serologic (i.e., antibody) testing as the sole basis for diagnosis of acute SARS-CoV-2 infection **(AIII)**.
• There is insufficient evidence for the Panel to recommend either for or against the use of SARS-CoV-2 serologic testing to assess for immunity or to guide clinical decisions about using COVID-19 vaccines or anti-SARS-CoV-2 monoclonal antibodies in certain people.

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

Diagnostic Testing for SARS-CoV-2 Infection

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

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

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

Although nasopharyngeal specimens remain the recommended samples for SARS-CoV-2 diagnostic testing, nasal (anterior nares or mid-turbinate) or oropharyngeal swabs are acceptable alternatives.[3] Lower respiratory tract samples have a higher yield than upper respiratory tract samples, but they

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

Nucleic Acid Amplification Testing for SARS-CoV-2 Infection

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

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

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

SARS-CoV-2 poses several diagnostic challenges, including the potential for discordant viral shedding between the upper and lower respiratory tract. However, due to the high specificity of NAATs, a positive result on a NAAT of an upper respiratory tract sample from a patient with recent onset of SARS-CoV-2-compatible symptoms is sufficient to diagnose COVID-19. In patients with COVID-19, severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS), lower respiratory tract specimens have a higher viral load and thus a higher yield than upper respiratory tract specimens.[8-13] For intubated or mechanically ventilated patients with clinical signs and symptoms that are consistent with COVID-19 pneumonia, the COVID-19 Treatment Guidelines Panel (the Panel) recommends obtaining lower respiratory tract samples to establish a diagnosis of COVID-19 if an initial upper respiratory tract sample is negative **(BII)**. The Panel recommends obtaining endotracheal aspirates over bronchial wash or bronchoalveolar lavage (BAL) samples when collecting lower respiratory tract samples to establish a diagnosis of COVID-19 **(BII)**.

BAL and sputum induction are aerosol-generating procedures that should be performed only after carefully considering the risk of exposing staff to infectious aerosols. Endotracheal aspiration appears to

carry a lower risk of aerosol generation than BAL, and some experts consider the sensitivity and specificity of endotracheal aspirates and BAL specimens comparable in detecting SARS-CoV-2.

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

NAATs can detect SARS-CoV-2 RNA in specimens obtained weeks to months after the onset of COVID-19 symptoms.[14,15] However, the likelihood of recovering replication-competent virus >10 days from the onset of symptoms in those with mild disease and >20 days in those with severe disease is very low.[16,17] Furthermore, both virologic studies and contact tracing of high-risk contacts show a low risk for SARS-CoV-2 transmission after these intervals.[18,19] Based on these results, the Centers for Disease Control and Prevention (CDC) recommends that NAATs should not be repeated in asymptomatic persons within 90 days of a previous SARS-CoV-2 infection, even if the person has had a significant exposure to SARS-CoV-2.[20] An exception to this is for health care workers who meet the specific criteria found in CDC guidance.[21] If there are concerns that an immunocompromised health care worker may still be infectious >20 days from the onset of SARS-CoV-2 infection, consulting local employee health services about return-to-work testing policies is advised.

SARS-CoV-2 reinfection has been reported in people after an initial diagnosis of infection; therefore, clinicians should consider using a NAAT for those who have recovered from a previous infection and who present with symptoms that are compatible with SARS-CoV-2 infection if there is no alternative diagnosis **(BIII)**. However, a negative result on an initial NAAT followed by a positive result on a subsequent test does not necessarily mean a person has been reinfected; this can occur due to intermittent detection of viral RNA.[14] When the results for an initial and a subsequent test are positive, comparative viral sequence data from both tests are needed to distinguish between the persistent presence of viral fragments and reinfection. In the absence of viral sequence data, the cycle threshold (Ct) value from a positive NAAT result may provide information about whether a newly detected infection is related to the persistence of viral fragments or to reinfection. The Ct value is the number of PCR cycles at which the nucleic acid target in the sample becomes detectable. In general, the Ct value is inversely related to the SARS-CoV-2 viral load. Because the clinical utility of Ct values is an area of active investigation, an expert should be consulted if these values are used to guide clinical decisions.

Antigen Testing for SARS-CoV-2 Infection

Antigen-based diagnostic tests (which detect viral antigens) are less sensitive than laboratory-based NAATs, but they have similarly high specificity. Antigen tests perform best early in the course of symptomatic SARS-CoV-2 infection, when the viral load is thought to be highest. Early data suggest that antigen tests can detect the Omicron variant, but they may have lower sensitivity to this variant compared to earlier variants.[22] Advantages of antigen tests include their low cost and rapid turnaround time. The availability of immediate results makes them an attractive option for point-of-care testing in high-risk congregate settings (e.g., long-term care facilities, schools, dormitories, correctional facilities) and community settings where preventing transmission is critical. These tests can also be used to inform decisions about the use of post-exposure prophylaxis (PEP). Antigen tests also allow for repeat testing to quickly identify persons with SARS-CoV-2 infection.

Increasingly, data are available to guide the use of antigen tests as screening tests to detect or exclude SARS-CoV-2 infection in asymptomatic persons, or to determine whether a person who was previously confirmed to have SARS-CoV-2 infection is still infectious. The CDC has developed an antigen testing algorithm for persons in congregate living settings and community settings who have symptoms of COVID-19, those who are asymptomatic and have a close contact with COVID-19, and those who are asymptomatic and have no known exposure to a person with COVID-19.[23] The CDC testing algorithm

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

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

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

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

Unlike NAATs and antigen tests for SARS-CoV-2 that detect the presence of the virus, serologic or antibody tests can detect recent or prior SARS-CoV-2 infection. Because it may take 21 days or longer after symptom onset for seroconversion to occur (i.e., the development of detectable immunoglobulin [Ig] M and/or IgG antibodies to SARS-CoV-2),[24-29] the Panel **does not recommend** using serologic testing as the sole basis for diagnosing acute SARS-CoV-2 infection **(AIII)**. Because NAATs and antigen tests for SARS-CoV-2 occasionally yield false negative results, serologic tests have been used in some settings as an additional diagnostic test for patients who are strongly suspected to have SARS-CoV-2 infection. Using a serologic test in combination with a NAAT to detect IgG or total antibodies 3 to 4 weeks after symptom onset maximizes the sensitivity and specificity to detect past infection.

No serologic tests for SARS-CoV-2 are approved by the FDA; some, but not all, commercially available serologic tests for SARS-CoV-2 have received EUAs from the FDA.[30] Several professional societies and federal agencies, including the Infectious Diseases Society of America, the CDC, and the FDA, provide guidance on the use of serologic testing for SARS-CoV-2.

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

- Important performance characteristics of many of the commercially available serologic tests have not been fully characterized, including the sensitivity and specificity of these tests (i.e., the rates of true positive and true negative results). Only serologic assays that have FDA EUAs should be used in public health or clinical settings. Formal comparisons of serologic tests are in progress.
- Two types of serologic tests have received EUAs from the FDA. The first type are antibody tests that detect the presence of binding antibodies, which bind to a pathogen (e.g., a virus). The second type detects neutralizing antibodies from recent or prior SARS-CoV-2 infection. It is unknown whether 1 type of test is more clinically meaningful than the other.
- Serologic assays may detect IgM, IgG, IgA, and/or total antibodies, or a combination of IgM and IgG antibodies. Serologic assays that detect IgG and total antibodies have higher specificity to detect past infection than assays that detect IgM and/or IgA antibodies or a combination of IgM and IgG antibodies.
- False positive test results may occur due to cross-reactivity from pre-existing antibodies to other coronaviruses.

Serologic Testing and Immunity to SARS-CoV-2 Infection

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

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

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

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

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

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

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

- Make decisions about how to group persons in congregate settings;
- Determine whether someone may return to the workplace; *or*
- Assess for immunity to SARS-CoV-2 following vaccination in immunocompetent individuals, except in clinical trials.

References

1. Centers for Disease Control and Prevention. Testing strategies for SARS-CoV-2. 2021. Available at: https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/sars-cov2-testing-strategies.html. Accessed February 28, 2022.
2. Food and Drug Administration. Coronavirus disease 2019 (COVID-19) emergency use authorizations for

medical devices. 2021. Available at: https://www.fda.gov/medical-devices/emergency-use-authorizations-medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices. Accessed February 28, 2022.

3. Centers for Disease Control and Prevention. Interim guidelines for collecting and handling of clinical specimens for COVID-19 testing. 2021. Available at: https://www.cdc.gov/coronavirus/2019-ncov/lab/guidelines-clinical-specimens.html. Accessed February 28, 2022.
4. Centers for Disease Control and Prevention. Nucleic acid amplification tests (NAATs). 2021. Available at: https://www.cdc.gov/coronavirus/2019-ncov/lab/naats.html. Accessed February 28, 2022.
5. Food and Drug Administration. Genetic variants of SARS-CoV-2 may lead to false negative results with molecular tests for detection of SARS-CoV-2—letter to clinical laboratory staff and health care providers. 2021. Available at: https://www.fda.gov/medical-devices/letters-health-care-providers/genetic-variants-sars-cov-2-may-lead-false-negative-results-molecular-tests-detection-sars-cov-2. Accessed February 28, 2022.
6. Kucirka LM, Lauer SA, Laeyendecker O, Boon D, Lessler J. Variation in false-negative rate of reverse transcriptase polymerase chain reaction-based SARS-CoV-2 tests by time since exposure. *Ann Intern Med*. 2020;173(4):262-267. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32422057.
7. Centers for Disease Control and Prevention. Science brief: emerging SARS-CoV-2 variants. 2021. Available at: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/scientific-brief-emerging-variants.html. Accessed March 21, 2022.
8. Chan PK, To WK, Ng KC, et al. Laboratory diagnosis of SARS. *Emerg Infect Dis*. 2004;10(5):825-831. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15200815.
9. Tang P, Louie M, Richardson SE, et al. Interpretation of diagnostic laboratory tests for severe acute respiratory syndrome: the Toronto experience. *CMAJ*. 2004;170(1):47-54. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14707219.
10. Memish ZA, Al-Tawfiq JA, Makhdoom HQ, et al. Respiratory tract samples, viral load, and genome fraction yield in patients with Middle East respiratory syndrome. *J Infect Dis*. 2014;210(10):1590-1594. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24837403.
11. Centers for Disease Control and Prevention. Interim guidelines for collecting, handling, and testing clinical specimens from persons under investigation (PUIs) for Middle East respiratory syndrome coronavirus (MERS-CoV)–Version 2.1. 2019. Available at: https://www.cdc.gov/coronavirus/mers/guidelines-clinical-specimens.html. Accessed March 21, 2022.
12. Hase R, Kurita T, Muranaka E, et al. A case of imported COVID-19 diagnosed by PCR-positive lower respiratory specimen but with PCR-negative throat swabs. *Infect Dis (Lond)*. 2020;52(6):423-426. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32238024.
13. Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in different types of clinical specimens. *JAMA*. 2020;323(18):1843-1844. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32159775.
14. Xiao AT, Tong YX, Zhang S. Profile of RT-PCR for SARS-CoV-2: a preliminary study from 56 COVID-19 patients. *Clin Infect Dis*. 2020;71(16):2249-2251. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32306036.
15. Rhee C, Kanjilal S, Baker M, Klompas M. Duration of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infectivity: when is it safe to discontinue isolation? *Clin Infect Dis*. 2021;72(8):1467-1474. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33029620.
16. Arons MM, Hatfield KM, Reddy SC, et al. Presymptomatic SARS-CoV-2 infections and transmission in a skilled nursing facility. *N Engl J Med*. 2020;382(22):2081-2090. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32329971.
17. Bullard J, Dust K, Funk D, et al. Predicting infectious severe acute respiratory syndrome coronavirus 2 from diagnostic samples. *Clin Infect Dis*. 2020;71(10):2663-2666. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32442256.

18. Cheng HY, Jian SW, Liu DP, et al. Contact tracing assessment of COVID-19 transmission dynamics in Taiwan and risk at different exposure periods before and after symptom onset. *JAMA Intern Med*. 2020;180(9):1156-1163. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32356867.

19. Korea Centers for Disease Control and Prevention. Findings from investigation and analysis of re-positive cases. 2020. Available at: https://www.mofa.go.kr/viewer/skin/doc.html?fn=20200521024820767.pdf&rs=/viewer/result/202203. Accessed March 21, 2022.

20. Centers for Disease Control and Prevention. Ending isolation and precautions for people with COVID-19: interim guidance. 2022. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/duration-isolation.html. Accessed March 21, 2022.

21. Centers for Disease Control and Prevention. Interim guidance for managing healthcare personnel with SARS-CoV-2 infection or exposure to SARS-CoV-2. 2022. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-risk-assesment-hcp.html. Accessed March 21, 2022.

22. Food and Drug Administration. SARS-CoV-2 viral mutations: impact on COVID-19 tests. 2021. Available at: https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/sars-cov-2-viral-mutations-impact-covid-19-tests. Accessed March 21, 2022.

23. Centers for Disease Control and Prevention. Guidance for antigen testing for SARS-CoV-2 for healthcare providers testing individuals in the community. 2022. Available at: https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antigen-tests-guidelines.html. Accessed February 28, 2022.

24. Guo L, Ren L, Yang S, et al. Profiling early humoral response to diagnose novel coronavirus disease (COVID-19). *Clin Infect Dis*. 2020;71(15):778-785. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32198501.

25. Haveri A, Smura T, Kuivanen S, et al. Serological and molecular findings during SARS-CoV-2 infection: the first case study in Finland, January to February 2020. *Euro Surveill*. 2020;25(11). Available at: https://www.ncbi.nlm.nih.gov/pubmed/32209163.

26. Long QX, Liu BZ, Deng HJ, et al. Antibody responses to SARS-CoV-2 in patients with COVID-19. *Nat Med*. 2020;26(6):845-848. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32350462.

27. Okba NMA, Muller MA, Li W, et al. Severe acute respiratory syndrome coronavirus 2-specific antibody responses in coronavirus disease patients. *Emerg Infect Dis*. 2020;26(7):1478-1488. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32267220.

28. Xiang F, Wang X, He X, et al. Antibody detection and dynamic characteristics in patients with coronavirus disease 2019. *Clin Infect Dis*. 2020;71(8):1930-1934. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32306047.

29. Zhao J, Yuan Q, Wang H, et al. Antibody responses to SARS-CoV-2 in patients with novel coronavirus disease 2019. *Clin Infect Dis*. 2020;71(16):2027-2034. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32221519.

30. Food and Drug Administration. EUA authorized serology test performance. 2021. Available at: https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/eua-authorized-serology-test-performance. Accessed February 28, 2022.

Prevention of SARS-CoV-2 Infection

Last Updated: March 24, 2022

Summary Recommendations

• The COVID-19 Treatment Guidelines Panel (the Panel) recommends COVID-19 vaccination as soon as possible for everyone who is eligible according to the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices **(AI)**.
• The Panel recommends using **tixagevimab 300 mg plus cilgavimab 300 mg (Evusheld)** administered as 2 consecutive 3 mL intramuscular injections **(BIII)** as SARS-CoV-2 pre-exposure prophylaxis (PrEP) for adults and adolescents (aged ≥12 years and weighing ≥40 kg) who do not have SARS-CoV-2 infection, who have not been recently exposed to an individual with SARS-CoV-2 infection, **AND** who:
  • Are moderately to severely immunocompromised and may have 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 reaction to a COVID-19 vaccine or any of its components.
• For patients who have previously received a dose of tixagevimab 150 mg plus cilgavimab 150 mg, the Food and Drug Administration Emergency Use Authorization states that a second dose of tixagevimab 150 mg plus cilgavimab 150 mg should be given as soon as possible.
• **Tixagevimab plus cilgavimab is not a substitute for COVID-19 vaccination and should not be used in unvaccinated individuals for whom COVID-19 vaccination is recommended and who are anticipated to have an adequate response.**
• If supplies of tixagevimab plus cilgavimab are limited, priority for use as PrEP should be given to those who are at the highest risk for severe COVID-19.
• 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 predominant variants circulating in the United States **(AIII)**.

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

General Prevention Measures

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

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

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

Vaccines

Vaccination is the most effective way to prevent SARS-CoV-2 infection. The COVID-19 Treatment Guidelines Panel (the Panel) recommends COVID-19 vaccination as soon as possible for everyone who is eligible according to CDC's Advisory Committee on Immunization Practices **(AI)**. Three vaccines are authorized or approved for use in the United States to prevent COVID-19. For primary and booster vaccinations, the mRNA vaccines (i.e., BNT162b2 [Pfizer-BioNTech] or mRNA-1273 [Moderna]) are preferable to the Ad26.COV2.S (Johnson & Johnson/Janssen) vaccine due to its risk of serious adverse events.[4] A primary series of COVID-19 vaccinations is recommended for everyone aged ≥5 years in the United States. Everyone aged ≥12 years should also receive a booster dose at least 5 months after completion of the primary series of an mRNA vaccine (BNT162b2 or mRNA-1273) or at least 2 months after receipt of the primary, single-dose Ad26.COV2.S vaccine.[5] The type and dose of vaccine and the timing of the primary and booster vaccinations depend on the recipient's age and underlying medical conditions. CDC regularly updates the clinical considerations for use of the COVID-19 vaccines currently approved by the Food and Drug Administration (FDA) or authorized for use in the United States.[6]

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.[7,8]

Reports have suggested that there is an increased risk of thrombosis with thrombocytopenia syndrome (TTS) in adults who have received the Ad26.COV2.S vaccine[8] and, rarely, the mRNA-1273 vaccine.[9] TTS is a rare but serious condition that causes blood clots in large blood vessels and low platelets. Women aged 30 to 49 years should be aware of the increased risk of this rare event. The American Society of Hematology and the American Heart Association/American Stroke Association Stroke Council leadership have published considerations that are relevant to the diagnosis and treatment of TTS that occurs in people who receive the Ad26.COV2.S vaccine. These considerations include information on administering a nonheparin anticoagulant and intravenous immunoglobulin to these patients.[10,11] Given the rarity of this syndrome and the unique treatment required, consider consulting a hematologist when treating these patients.

Myocarditis and pericarditis after COVID-19 vaccination are rare, and most of the reported cases were very mild and self-limiting. These conditions have occurred most often in male adolescents, young adults, and people who have received mRNA vaccines.[12]

Guillain-Barré syndrome (GBS) in people who received the Ad26.COV2.S vaccine is rare. GBS is a neurologic disorder that causes muscle weakness and sometimes paralysis. Most people with GBS fully recover, but some have permanent nerve damage. Onset typically occurs about 2 weeks after vaccination. GBS has mostly been reported in men aged ≥50 years.[12]

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

Vaccination in Pregnant or Lactating People

Pregnant and lactating individuals were not included in the initial COVID-19 vaccine trials. However, CDC, the American College of Obstetricians and Gynecologists (ACOG), and the Society for Maternal-Fetal Medicine recommend vaccination for pregnant and lactating people based on the accumulated

safety and efficacy data on the use of these vaccines in pregnant people, as well as the increased risk of severe disease in pregnant individuals with COVID-19. These organizations also recommend vaccination for people who are trying to become pregnant now or who may become pregnant in the future.[13-18] The ACOG publication includes a guide to assist clinicians during conversations about COVID-19 vaccination with pregnant patients.[19]

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. Other individuals may not have been fully vaccinated because of a history of a severe adverse reaction to a COVID-19 vaccine or its components.

Based on the results of PROVENT, a large randomized controlled trial (ClinicalTrials.gov Identifier NCT04625725) conducted when the major circulating SARS-CoV-2 variants were Alpha (B.1.1.7), Beta (B.1.351), Delta (B.1.617.2), and Epsilon (B.1.429), the FDA issued an Emergency Use Authorization (EUA) for the anti-SARS-CoV-2 monoclonal antibodies (mAbs) tixagevimab plus cilgavimab (Evusheld) as pre-exposure prophylaxis (PrEP) for certain individuals at high risk of progressing to severe COVID-19 if they become infected with SARS-CoV-2.[20] A modification in the fragment crystallizable (Fc) region gives these anti-SARS-CoV-2 mAbs prolonged half-lives, resulting in potential protection from SARS-CoV-2 infection for up to 6 months, depending on the variant.

The dose used in the PROVENT trial was tixagevimab 150 mg plus cilgavimab 150 mg, which was the dose initially authorized by the FDA. Recent in vitro data showed that the BA.1 and BA.1.1 subvariants of the Omicron variant, which are the predominant variants circulating in the United States, have decreased susceptibility to tixagevimab plus cilgavimab.[20-23] Because of these findings, on February 24, 2022, the FDA revised the EUA to authorize tixagevimab 300 mg plus cilgavimab 300 mg as the dose for individuals receiving these anti-SARS-CoV-2 mAbs for the first time.[20] For those who received the dose initially authorized by the FDA, the revised FDA authorization recommends administration of an additional dose of tixagevimab 150 mg plus cilgavimab 150 mg as soon as possible. The Omicron BA.2 subvariant is now emerging and has been shown in vitro to retain near-full susceptibility to tixagevimab plus cilgavimab.[20,23,24] If Omicron BA.2 becomes the predominant variant in select regions, dose recommendations could be further refined in the future.

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

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

from TACKLE, a Phase 3 clinical trial for the treatment of patients with mild to moderate COVID-19.[25]

- The tixagevimab 150 mg plus cilgavimab 150 mg dose initially authorized by the FDA may not be sufficient for preventing COVID-19 caused by the Omicron BA.1 and BA.1.1 subvariants. No clinical data, and limited PK/PD data, guide the administration of repeat doses of tixagevimab 150 mg plus cilgavimab 150 mg. It is unknown whether the amount of time between the initial and repeat doses of tixagevimab 150 mg plus cilgavimab 150 mg alters the duration of protection against the Omicron BA.1 and BA.1.1 subvariants.

Factoring in the limitations outlined above:

- The Panel recommends using **tixagevimab 300 mg plus cilgavimab 300 mg** administered as 2 consecutive 3 mL intramuscular (IM) injections **(BIII)** as SARS-CoV-2 PrEP for adults and adolescents (aged ≥12 years and weighing ≥40 kg) who do not have SARS-CoV-2 infection, who have not been recently exposed to an individual with SARS-CoV-2 infection, who have not previously received this regimen, **AND** who:
  - Are moderately to severely immunocompromised and may have 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 reaction to a COVID-19 vaccine or any of its components.
- For patients who have previously received a dose of tixagevimab 150 mg plus cilgavimab 150 mg, the FDA EUA states that a second dose of tixagevimab 150 mg plus cilgavimab 150 mg should be given as soon as possible.
- **Tixagevimab plus cilgavimab is not a substitute for COVID-19 vaccination and should not be used in unvaccinated individuals for whom COVID-19 vaccination is recommended and who are anticipated to have an adequate response.**

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

- Are receiving active treatment for solid tumors and hematologic malignancies.
- Received a solid organ transplant and are receiving immunosuppressive therapy.
- Received chimeric antigen receptor T cell therapy or a hematopoietic stem cell transplant (within 2 years of transplantation or receiving immunosuppression therapy).
- Have a moderate or severe primary immunodeficiency (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome).
- Have advanced or untreated HIV infection (defined as people with HIV and CD4 T lymphocyte counts <200 cells/mm^3, a history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV).
- Are receiving active treatment with high-dose corticosteroids (i.e., ≥20 mg prednisone or equivalent per day when administered for ≥2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumor-necrosis blockers, or other immunosuppressive or immunomodulatory biologic agents (e.g., B cell–depleting agents).

Additional Considerations

- Because there are no clinical efficacy data available for tixagevimab 300 mg plus cilgavimab 300 mg, and there are uncertainties about the extent and duration of protection against the Omicron

BA.1 and BA.1.1 subvariants, high-risk individuals who receive PrEP should continue to use other measures to protect themselves from infection, especially if these subvariants are circulating within their communities.

- The strength of the Panel's recommendation for tixagevimab 300 mg plus cilgavimab 300 mg is based partly on PK/PD modeling for the Omicron BA.1 and BA.1.1 subvariants and on the anticipation that the susceptible BA.2 subvariant will soon become dominant in the United States.
- 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.[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 = 3,441) or placebo (administered as 2 IM injections; n = 1,731). The primary endpoint was symptomatic SARS-CoV-2 infection and a positive RT-PCR result during the 183 days of follow-up.

During the study, once COVID-19 vaccines became available, participants could choose to be unblinded and receive the vaccine. 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 6.5 months showed a similar relative risk reduction for symptomatic infection in the tixagevimab plus cilgavimab arm.

Adverse events were reported for 35% of participants in the tixagevimab plus cilgavimab arm and 34% of participants in the placebo arm. Serious adverse events were reported in 1% of participants in each arm; 1 participant in the tixagevimab plus cilgavimab arm had an anaphylactic reaction that was resolved with epinephrine therapy. The incidence of adverse events was similar in both study arms; most events were mild (73%) or moderate (24%). Rare, serious cardiac adverse events occurred in 0.6% of participants in the tixagevimab plus cilgavimab arm and in 0.2% 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 mAbs.

TACKLE was a Phase 3 trial 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 was 84 days). Adverse events were reported for 29% of participants in the tixagevimab plus cilgavimab arm

and for 36% of participants in the placebo arm; the majority of events were mild to moderate in severity. Serious cardiac adverse events were reported for 4 participants; 3 had received tixagevimab plus cilgavimab and 1 had received placebo. All events occurred in participants who had cardiac risk factors or a history of cardiovascular disease.[20]

Other Drugs for Pre-Exposure Prophylaxis

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

Clinical trials are investigating several agents, including emtricitabine plus tenofovir alafenamide or tenofovir disoproxil fumarate, hydroxychloroquine, ivermectin, and supplements such as zinc, vitamin C, and vitamin D. Please check ClinicalTrials.gov for the latest information.

Hydroxychloroquine, given at different doses and durations, has been studied in randomized controlled trials to assess whether it could prevent SARS-CoV-2 infection in those at risk for being exposed to infected individuals, such as health care workers. One study reported no evidence of a benefit of hydroxychloroquine, and it was ultimately halted due to futility before it reached its target enrollment.[26] In another hydroxychloroquine study, which also did not meet its target enrollment and was stopped early, the majority of the potential transmission events were not confirmed by virologic testing.[27] Neither study demonstrated any evidence of a reduction in 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, which is not susceptible to these agents, is currently the predominant variant circulating in the United States **(AIII)**.

Vaccination remains a highly effective way to prevent SARS-CoV-2 infection. However, despite 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 predominant variant currently circulating in the United States is the Omicron variant. The Panel **recommends against** the use of these anti-SARS-CoV-2 mAbs because the Omicron variant is not susceptible to them **(AIII)**.

Chloroquine and Hydroxychloroquine

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

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

Other Drugs for Post-Exposure Prophylaxis

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

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

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

In a descriptive, uncontrolled, interventional study of 33 contacts of patients with laboratory-confirmed COVID-19, no cases of SARS-CoV-2 infection were identified within 21 days of initiating ivermectin for PEP.[37] In a small, case-control study in SARS-CoV-2-exposed health care workers, 186 participants who became infected were matched with 186 uninfected controls. Of those who received ivermectin after exposure to SARS-CoV-2, 38 were in the infected group and 77 were in the uninfected group, which led the investigators to conclude that ivermectin reduced the incidence of SARS-CoV-2 infection.[38]

References

1. Centers for Disease Control and Prevention. Scientific brief: SARS-CoV-2 transmission. 2021. Available at: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/sars-cov-2-transmission.html. Accessed March 18, 2022.
2. Centers for Disease Control and Prevention. COVID-19: how to protect yourself & others. 2021. Available at: https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html. Accessed March 18, 2022.
3. Centers for Disease Control and Prevention. Infection control guidance for healthcare professionals about coronavirus (COVID-19). 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/infection-control.html. Accessed March 18, 2022.
4. Centers for Disease Control and Prevention. Johnson & Johnson's Janssen COVID-19 vaccine overview and safety. 2022. Available at: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/janssen.html. Accessed January 26, 2022.
5. Centers for Disease Control and Prevention. Stay up to date with your COVID-19 vaccines. 2022. Available at: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines.html. Accessed March 22, 2022.
6. Centers for Disease Control and Prevention. Use of COVID-19 vaccines in the United States: interim clinical considerations. 2022. Available at: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html. Accessed March 21, 2022.
7. Centers for Disease Control and Prevention. Interim considerations: preparing for the potential management of anaphylaxis after COVID-19 vaccination. 2020. Available at: https://www.cdc.gov/vaccines/covid-19/info-by-product/pfizer/anaphylaxis-management.html. Accessed March 22, 2022.
8. Food and Drug Administration. Fact sheet for healthcare providers administering vaccine (vaccination providers): emergency use authorization (EUA) of the Janssen COVID-19 vaccine to prevent coronavirus disease 2019 (COVID-19). 2022. Available at: https://www.fda.gov/media/146304/download.
9. See I, Lale A, Marquez P, et al. Case series of thrombosis with thrombocytopenia syndrome after COVID-19 vaccination—United States, December 2020 to August 2021. *Ann Intern Med*. 2022. Available at:

https://www.ncbi.nlm.nih.gov/pubmed/35038274.

10. American Society of Hematology. Vaccine-induced immune thrombotic thrombocytopenia. 2022. Available at: https://www.hematology.org/covid-19/vaccine-induced-immune-thrombotic-thrombocytopenia. Accessed March 22, 2022.
11. Furie KL, Cushman M, Elkind MSV, et al. Diagnosis and management of cerebral venous sinus thrombosis with vaccine-induced immune thrombotic thrombocytopenia. *Stroke*. 2021;52(7):2478-2482. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33914590.
12. Centers for Disease Control and Prevention. Selected adverse events reported after COVID-19 vaccination. 2022. Available at: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html. Accessed March 22, 2022.
13. Centers for Disease Control and Prevention. COVID-19 vaccines while pregnant or breastfeeding. 2022. Available at: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/pregnancy.html. Accessed March 22, 2022.
14. Society for Maternal-Fetal Medicine. Publications and clinical guidance. 2022. Available at: https://www.smfm.org/covidclinical. Accessed March 22, 2022.
15. Shimabukuro TT, Kim SY, Myers TR, et al. Preliminary findings of mRNA COVID-19 vaccine safety in pregnant persons. *N Engl J Med*. 2021;384(24):2273-2282. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33882218.
16. Zauche LH, Wallace B, Smoots AN, et al. Receipt of mRNA COVID-19 vaccines and risk of spontaneous abortion. *N Engl J Med*. 2021;385(16):1533-1535. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34496196.
17. Goldshtein I, Nevo D, Steinberg DM, et al. Association between BNT162b2 vaccination and incidence of SARS-CoV-2 infection in pregnant women. *JAMA*. 2021;326(8):728-735. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34251417.
18. Collier AY, McMahan K, Yu J, et al. Immunogenicity of COVID-19 mRNA vaccines in pregnant and lactating women. *JAMA*. 2021;325(23):2370-2380. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33983379.
19. The American College of Obstetricians and Gynecologists. Practice advisory: COVID-19 vaccination considerations for obstetric-gynecologic care. 2020. Available at: https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2020/12/vaccinating-pregnant-and-lactating-patients-against-covid-19. Accessed March 22, 2022.
20. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for Evusheld (tixagevimab co-packaged with cilgavimab). 2022. Available at: https://www.fda.gov/media/154701/download.
21. Cameroni E, Bowen JE, Rosen LE, et al. Broadly neutralizing antibodies overcome SARS-CoV-2 Omicron antigenic shift. *Nature*. 2022;602(7898):664-670. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35016195.
22. Takashita E, Kinoshita N, Yamayoshi S, et al. Efficacy of antibodies and antiviral drugs against Covid-19 omicron variant. *N Engl J Med*. 2022;386(10):995-998. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35081300.
23. Iketani S, Liu L, Guo Y, et al. Antibody evasion properties of SARS-CoV-2 omicron sublineages. *bioRxiv*. 2022;Preprint. Available at: https://www.biorxiv.org/content/10.1101/2022.02.07.479306v1.
24. Takashita E, Kinoshita N, Yamayoshi S, et al. Efficacy of antiviral agents against the SARS-CoV-2 omicron subvariant BA.2. *N Engl J Med*. 2022. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35263535.
25. Food and Drug Administration. Emergency Use Authorization (EUA) for Evusheld. 2022. Available at: https://www.fda.gov/media/156674/download.
26. Abella BS, Jolkovsky EL, Biney BT, et al. Efficacy and safety of hydroxychloroquine vs placebo for pre-exposure SARS-CoV-2 prophylaxis among health care workers: a randomized clinical trial. *JAMA Intern Med*.

2021;181(2):195-202. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33001138.

27. Rajasingham R, Bangdiwala AS, Nicol MR, et al. Hydroxychloroquine as pre-exposure prophylaxis for coronavirus disease 2019 (COVID-19) in healthcare workers: a randomized trial. *Clin Infect Dis*. 2021;72(11):e835-e843. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33068425.
28. Yao X, Ye F, Zhang M, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Clin Infect Dis*. 2020;71(15):732-739. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32150618.
29. Vincent MJ, Bergeron E, Benjannet S, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. *Virol J*. 2005;2:69. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16115318.
30. Lee SH, Son H, Peck KR. Can post-exposure prophylaxis for COVID-19 be considered as an outbreak response strategy in long-term care hospitals? *Int J Antimicrob Agents*. 2020;55(6):105988. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32305587.
31. Barnabas RV, Brown ER, Bershteyn A, et al. Hydroxychloroquine as postexposure prophylaxis to prevent severe acute respiratory syndrome coronavirus 2 infection: a randomized trial. *Ann Intern Med*. 2021;174(3):344-352. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33284679.
32. Boulware DR, Pullen MF, Bangdiwala AS, et al. A randomized trial of hydroxychloroquine as postexposure prophylaxis for COVID-19. *N Engl J Med*. 2020;383(6):517-525. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32492293.
33. Mitja O, Corbacho-Monne M, Ubals M, et al. A cluster-randomized trial of hydroxychloroquine for prevention of COVID-19. *N Engl J Med*. 2021;384(5):417-427. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33289973.
34. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res*. 2020;178:104787. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32251768.
35. Belhadjer Z, Meot M, Bajolle F, et al. Acute heart failure in multisystem inflammatory syndrome in children in the context of global SARS-CoV-2 pandemic. *Circulation*. 2020;142(5):429-436. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32418446.
36. Hellwig MD, Maia A. A COVID-19 prophylaxis? Lower incidence associated with prophylactic administration of ivermectin. *Int J Antimicrob Agents*. 2021;57(1):106248. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33259913.
37. Aguirre Chang G FA. COVID-19: post-exposure prophylaxis with ivermectin in contacts. At homes, places of work, nursing homes, prisons, and others. *ResearchGate*. 2020;Preprint. Available at: https://www.researchgate.net/publication/344781515_COVID-19_POST-EXPOSURE_PROPHYLAXIS_WITH_IVERMECTIN_IN_CONTACTS.
38. Behera P, Patro BK, Singh AK, et al. Role of ivermectin in the prevention of SARS-CoV-2 infection among healthcare workers in India: a matched case-control study. *PLoS One*. 2021;16(2):e0247163. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33592050.

Clinical Spectrum of SARS-CoV-2 Infection

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Patients with SARS-CoV-2 infection can experience a range of clinical manifestations, from no symptoms to critical illness. In general, adults with SARS-CoV-2 infection can be grouped into the following severity of illness categories; however, the criteria for each category may overlap or vary across clinical guidelines and clinical trials, and a patient's clinical status may change over time.

- *Asymptomatic or Presymptomatic Infection:* Individuals who test positive for SARS-CoV-2 using a virologic test (i.e., a nucleic acid amplification test [NAAT] or an antigen test) but who have no symptoms that are consistent with COVID-19.
- *Mild Illness:* Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging.
- *Moderate Illness:* Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation (SpO_2) ≥94% on room air at sea level.
- *Severe Illness:* Individuals who have SpO_2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mm Hg, a respiratory rate >30 breaths/min, or lung infiltrates >50%.
- *Critical Illness:* Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

Patients with certain underlying comorbidities are at a higher risk of progressing to severe COVID-19. These comorbidities include being aged ≥65 years; having cardiovascular disease, chronic lung disease, sickle cell disease, diabetes, cancer, obesity, or chronic kidney disease; being pregnant; being a cigarette smoker; being a transplant recipient; and receiving immunosuppressive therapy.[1] Health care providers should monitor such patients closely until clinical recovery is achieved.

The optimal pulmonary imaging technique has not yet been defined for people with symptomatic SARS-CoV-2 infection. Initial evaluation for these patients may include a chest X-ray, ultrasound screening, or, if indicated, a computed tomography scan. An electrocardiogram should be performed if indicated. Laboratory testing includes a complete blood count with differential and a metabolic profile, including liver and renal function tests. Although inflammatory markers such as C-reactive protein (CRP), D-dimer, and ferritin are not routinely measured as part of standard care, results from such measurements may have prognostic value.[2-4]

The definitions for the severity of illness categories listed above also apply to pregnant patients. However, the threshold for certain interventions may be different for pregnant patients and nonpregnant patients. For example, oxygen supplementation is recommended for pregnant patients when SpO_2 falls below 95% on room air at sea level to accommodate physiologic changes in oxygen demand during pregnancy and to ensure adequate oxygen delivery to the fetus.[5] If laboratory parameters are used for monitoring pregnant patients and making decisions about interventions, clinicians should be aware that normal physiologic changes during pregnancy can alter several laboratory values. In general, leukocyte cell count increases throughout gestation and delivery and peaks during the immediate postpartum period. This increase is mainly due to neutrophilia.[6] D-dimer and CRP levels also increase during pregnancy and are often higher in pregnant patients than nonpregnant patients.[7] Detailed information on treating COVID-19 in pregnant patients can be found in Special Considerations in Pregnancy and in the pregnancy considerations subsection of each section of the Guidelines.

In pediatric patients, radiographic abnormalities are common and, for the most part, should not be the only criteria used to determine the severity of illness. The normal values for respiratory rate also vary with age in children; therefore, hypoxemia should be the primary criterion used to define severe COVID-19, especially in younger children. In a small number of children and in some young adults, SARS-CoV-2 infection may be followed by a severe inflammatory condition called multisystem inflammatory syndrome in children (MIS-C).[8,9] This syndrome is discussed in detail in Special Considerations in Children.

Asymptomatic or Presymptomatic Infection

Asymptomatic SARS-CoV-2 infection can occur, although the percentage of patients who remain truly asymptomatic throughout the course of infection is variable and incompletely defined. It is unclear what percentage of individuals who present with asymptomatic infection progress to clinical disease. Some asymptomatic individuals have been reported to have objective radiographic findings that are consistent with COVID-19 pneumonia.[10,11] Increasing the availability of virologic testing for SARS-CoV-2 and reliable serologic assays for SARS-CoV-2 antibodies will help determine the true prevalence of asymptomatic and presymptomatic infection. See Therapeutic Management of Nonhospitalized Adults With COVID-19 for recommendations regarding SARS-CoV-2-specific therapy.

Mild Illness

Patients with mild illness may exhibit a variety of signs and symptoms (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell). They do not have shortness of breath, dyspnea on exertion, or abnormal imaging. Most mildly ill patients can be managed in an ambulatory setting or at home through telemedicine or telephone visits. No imaging or specific laboratory evaluations are routinely indicated in otherwise healthy patients with mild COVID-19. Older patients and those with underlying comorbidities are at higher risk of disease progression; therefore, health care providers should monitor these patients closely until clinical recovery is achieved. See Therapeutic Management of Nonhospitalized Adults With COVID-19 for recommendations regarding SARS-CoV-2-specific therapy.

Moderate Illness

Moderate illness is defined as evidence of lower respiratory disease during clinical assessment or imaging, with SpO_2 ≥94% on room air at sea level. Given that pulmonary disease can progress rapidly in patients with COVID-19, patients with moderate disease should be closely monitored. If bacterial pneumonia or sepsis is suspected, administer empiric antibiotic treatment, re-evaluate the patient daily, and de-escalate or stop antibiotics if there is no evidence of bacterial infection. See Therapeutic Management of Nonhospitalized Adults With COVID-19 for recommendations regarding SARS-CoV-2-specific therapy.

Severe Illness

Patients with COVID-19 are considered to have severe illness if they have SpO_2 <94% on room air at sea level, PaO_2/FiO_2 <300 mm Hg, a respiratory rate >30 breaths/min, or lung infiltrates >50%. These patients may experience rapid clinical deterioration. Oxygen therapy should be administered immediately using a nasal cannula or a high-flow oxygen device. See Therapeutic Management of Hospitalized Adults With COVID-19 for recommendations regarding SARS-CoV-2-specific therapy. If secondary bacterial pneumonia or sepsis is suspected, administer empiric antibiotics, re-evaluate the patient daily, and de-escalate or stop antibiotics if there is no evidence of bacterial infection.

Critical Illness

Critically ill patients may have acute respiratory distress syndrome, septic shock that may represent virus-induced distributive shock, cardiac dysfunction, an exaggerated inflammatory response, and/or exacerbation of underlying comorbidities. In addition to pulmonary disease, patients with critical illness may also experience cardiac, hepatic, renal, central nervous system, or thrombotic disease.

As with any patient in the intensive care unit (ICU), successful clinical management of a patient with COVID-19 includes treating both the medical condition that initially resulted in ICU admission and other comorbidities and nosocomial complications. For more information, see Care of Critically Ill Adult Patients With COVID-19.

Infectious Complications in Patients With COVID-19

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

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

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

SARS-CoV-2 Reinfection

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

It has been speculated that reinfection may occur more frequently in those who have a less robust immune response during the initial infection, as is often reported in those with mild illness. Reinfection may also occur as initial immune responses wane over time. Nevertheless, one review noted that SARS-CoV-2 reinfection occurred after previous severe disease in three cases and as early as 3 weeks after the initial infection was diagnosed.[31] A public site that posts a variety of published and unpublished reports of reinfection notes that reinfection has occurred anywhere from a few weeks to many months after the initial infection, and it occasionally follows episodes of severe COVID-19.[32] Although data are limited, there is no evidence to suggest that the treatment of suspected or documented SARS-CoV-2 reinfection should be different from the treatment used during the initial infection, as outlined in Therapeutic Management of Nonhospitalized Adults With COVID-19 and Therapeutic Management of Hospitalized Adults With COVID-19.

Persistent Symptoms or Organ Dysfunction After Acute COVID-19

There have been an increasing number of reports of patients who experience persistent symptoms and/or organ dysfunction after acute COVID-19. Data about the incidence, natural history, and etiology of these symptoms are emerging. However, these reports have several limitations. For example, there is currently no agreed-upon case definition for persistent symptoms or organ dysfunction after acute COVID-19. In addition, most of these reports only included patients who attended post-COVID-19 clinics, and they often lack comparator groups. No specific treatments for the persistent effects of COVID-19 have yet been identified, although this COVID-19 rapid guideline proposes general management strategies.

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

Some of the symptoms overlap with the post-intensive care syndrome (PICS) that has been described in patients without COVID-19, but prolonged symptoms and disabilities after COVID-19 have also been reported in patients with milder illness, including outpatients (see General Considerations for information on PICS).[37,38]

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

CDC conducted a telephone survey of a random sample of 292 adult outpatients who had positive polymerase chain reaction results for SARS-CoV-2. Among the 274 respondents who were symptomatic at the time of testing, 35% reported not having returned to their usual state of health 2 weeks or more after testing; this included 26% of patients aged 18 to 34 years, 32% of those aged 35 to 49 years, and 47% of those aged ≥50 years.[38] An age of ≥50 years and the presence of three or more chronic medical conditions were associated with not returning to usual health within 14 to 21 days. Moreover, one in five individuals aged 18 to 34 years who did not have chronic medical conditions had not returned to baseline health when interviewed at a median of 16 days from the testing date.

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

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

Persistent symptoms after acute COVID-19 have also been reported in pregnant people.[43] Systematic data on persistent symptoms in children following recovery from the acute phase of COVID-19 are not currently available, although case reports suggest that children may experience long-term effects similar to those experienced by adults after clinical COVID-19.[44,45] MIS-C is discussed in Special Considerations in Children.

Fatigue

The prevalence of fatigue among 128 individuals from Ireland who had recovered from the acute phase of COVID-19 was examined using the Chalder Fatigue Scale (CFQ11). More than half of patients (67 of 128 patients [52.3%]) reported persistent fatigue at a median of 10 weeks after initial symptoms first appeared. There was no association between illness severity and fatigue.[46] An outpatient service that was developed in Italy for patients recovering from acute COVID-19 reported that 87% of 143 patients surveyed had persistent symptoms for a mean of 60 days after symptom onset. The most common symptom was fatigue, which occurred in 53.1% of these patients.[36]

Cardiopulmonary

A study from the United Kingdom reported that among 100 hospitalized patients with COVID-19 (32 received care in the ICU and 68 received care in hospital wards only), 72% of the ICU patients and 60% of the ward patients experienced fatigue and breathlessness at 4 to 8 weeks after hospital discharge. The authors suggested that posthospital rehabilitation may be necessary for some of these patients.[39] A retrospective study from China found that pulmonary function (as measured by spirometry) was still impaired 1 month after hospital discharge in 31 of 57 patients (54.4%) with COVID-19.[47] In a study

from Germany that included 100 patients who had recently recovered from COVID-19, cardiac magnetic resonance imaging (MRI) performed a median of 71 days after diagnosis revealed cardiac involvement in 78% of patients and ongoing myocardial inflammation in 60% of patients.[48] A retrospective study from China of 26 patients who had recovered from COVID-19 and who had initially presented with cardiac symptoms found abnormalities on cardiac MRI in 15 patients (58%).[49] This assessment of the prevalence of cardiac abnormalities in people with PASC should be viewed with caution, however, as the analysis included only patients with cardiac symptoms.

Neuropsychiatric

Neurologic and psychiatric symptoms have also been reported among patients who have recovered from acute COVID-19. High rates of anxiety and depression have been reported in some patients using self-report scales for psychiatric distress.[40,50] Younger patients have been reported to experience more psychiatric symptoms than patients aged >60 years.[39,40] Patients may continue to experience headaches, vision changes, hearing loss, loss of taste or smell, impaired mobility, numbness in extremities, tremors, myalgia, memory loss, cognitive impairment, and mood changes for up to 3 months after diagnosis of COVID-19.[51-53] One study in the United Kingdom administered cognitive tests to 84,285 participants who had recovered from suspected or confirmed SARS-CoV-2 infection. These participants had worse performances across multiple domains than would be expected for people with the same ages and demographic profiles; this effect was observed even among those who had not been hospitalized.[54] However, the study authors did not report when the tests were administered in relation to the diagnosis of COVID-19.

More research and more rigorous observational cohort studies are needed to better understand the pathophysiology and clinical course of post-acute COVID-19 sequelae and to identify management strategies for patients. More information about ongoing studies can be found at ClinicalTrials.gov.

References

1. Centers for Disease Control and Prevention. COVID-19 (coronavirus disease): people with certain medical conditions. 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Accessed August 31, 2021.
2. Tan C, Huang Y, Shi F, et al. C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. *J Med Virol*. 2020;92(7):856-862. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32281668.
3. Berger JS, Kunichoff D, Adhikari S, et al. Prevalence and outcomes of D-dimer elevation in hospitalized patients with COVID-19. *Arterioscler Thromb Vasc Biol*. 2020;40(10):2539-2547. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32840379.
4. Casas-Rojo JM, Anton-Santos JM, Millan-Nunez-Cortes J, et al. Clinical characteristics of patients hospitalized with COVID-19 in Spain: results from the SEMI-COVID-19 Registry. *Rev Clin Esp*. 2020;220(8):480-494. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32762922.
5. Society for Maternal Fetal Medicine. Management considerations for pregnant patients with COVID-19. 2020. Available at: https://s3.amazonaws.com/cdn.smfm.org/media/2336/SMFM_COVID_Management_of_COVID_pos_preg_patients_4-30-20_final.pdf.
6. Abbassi-Ghanavati M, Greer LG, Cunningham FG. Pregnancy and laboratory studies: a reference table for clinicians. *Obstet Gynecol*. 2009;114(6):1326-1331. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19935037.
7. Anderson BL, Mendez-Figueroa H, Dahlke JD, Raker C, Hillier SL, Cu-Uvin S. Pregnancy-induced changes in immune protection of the genital tract: defining normal. *Am J Obstet Gynecol*. 2013;208(4):321 e321-329. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23313311.

8. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet*. 2020;395(10237):1607-1608. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32386565.
9. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet*. 2020;395(10239):1771-1778. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32410760.
10. Zhang R, Ouyang H, Fu L, et al. CT features of SARS-CoV-2 pneumonia according to clinical presentation: a retrospective analysis of 120 consecutive patients from Wuhan city. *Eur Radiol*. 2020;30(8):4417-4426. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32279115.
11. Inui S, Fujikawa A, Jitsu M, et al. Chest CT findings in cases from the cruise ship "Diamond Princess" with coronavirus disease 2019 (COVID-19). *Radiology: Cardiothoracic Imaging*. 2020;2(2). Available at: https://pubs.rsna.org/doi/10.1148/ryct.2020200110.
12. Kim D, Quinn J, Pinsky B, Shah NH, Brown I. Rates of co-infection between SARS-CoV-2 and other respiratory pathogens. *JAMA*. 2020;323(20):2085-2086. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32293646.
13. Kubin CJ, McConville TH, Dietz D, et al. Characterization of bacterial and fungal infections in hospitalized patients with coronavirus disease 2019 and factors associated with health care-associated infections. *Open Forum Infect Dis*. 2021;8(6):ofab201. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34099978.
14. Garg N, Lee YI. Reactivation TB with severe COVID-19. *Chest*. 2020;158(4). Available at: https://journal.chestnet.org/article/S0012-3692(20)32910-X/fulltext.
15. Rodriguez-Tajes S, Miralpeix A, Costa J, et al. Low risk of hepatitis B reactivation in patients with severe COVID-19 who receive immunosuppressive therapy. *J Viral Hepat*. 2021;28(1):89-94. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32969557.
16. Aldhaleei WA, Alnuaimi A, Bhagavathula AS. COVID-19 induced hepatitis B virus reactivation: a novel case from the United Arab Emirates. *Cureus*. 2020;12(6):e8645. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32550096.
17. Xu R, Zhou Y, Cai L, et al. Co-reactivation of the human herpesvirus alpha subfamily (herpes simplex virus-1 and varicella zoster virus) in a critically ill patient with COVID-19. *Br J Dermatol*. 2020;183(6):1145-1147. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32790074.
18. Lier AJ, Tuan JL, Davis MW, et al. Case report: disseminated strongyloidiasis in a patient with COVID-19. *Am J Trop Med Hyg*. 2020;103(4):1590-1592. Available at: https://pubmed.ncbi.nlm.nih.gov/32830642.
19. Marchese V, Crosato V, Gulletta M, et al. Strongyloides infection manifested during immunosuppressive therapy for SARS-CoV-2 pneumonia. *Infection*. 2021;49(3):539-542. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32910321.
20. Stauffer WM, Alpern JD, Walker PF. COVID-19 and dexamethasone: a potential strategy to avoid steroid-related strongyloides hyperinfection. *JAMA*. 2020;324(7):623-624. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32761166.
21. Salmanton-Garcia J, Sprute R, Stemler J, et al. COVID-19-associated pulmonary aspergillosis, March–August 2020. *Emerg Infect Dis*. 2021;27(4):1077-1086. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33539721.
22. Chong WH, Neu KP. Incidence, diagnosis and outcomes of COVID-19-associated pulmonary aspergillosis (CAPA): a systematic review. *J Hosp Infect*. 2021;113:115-129. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33891985.
23. Machado M, Valerio M, Alvarez-Uria A, et al. Invasive pulmonary aspergillosis in the COVID-19 era: An expected new entity. *Mycoses*. 2021;64(2):132-143. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33210776.
24. Yusuf E, Seghers L, Hoek RAS, van den Akker JPC, Bode LGM, Rijnders BJA. Aspergillus in critically ill

COVID-19 patients: a scoping review. *J Clin Med*. 2021;10(11). Available at: https://www.ncbi.nlm.nih.gov/pubmed/34199528.

25. Singh AK, Singh R, Joshi SR, Misra A. Mucormycosis in COVID-19: a systematic review of cases reported worldwide and in India. *Diabetes Metab Syndr*. 2021;15(4):102146. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34192610.
26. Pal R, Singh B, Bhadada SK, et al. COVID-19-associated mucormycosis: an updated systematic review of literature. *Mycoses*. 2021;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34133798.
27. Cohen J, Burbelo PD. Reinfection with SARS-CoV-2: implications for vaccines. *Oxford Clin Infect Dis*. 2020;Published online ahead of print. Available at: https://pubmed.ncbi.nlm.nih.gov/33338197.
28. Nonaka CKV, Franco MM, Graf T, et al. Genomic evidence of SARS-CoV-2 reinfection case with E484K spike mutation, Brazil. *Emerg Infect Dis*. 2021;27(5). Available at: https://www.ncbi.nlm.nih.gov/pubmed/33605869.
29. Centers for Disease Control and Prevention. Interim guidance on duration of isolation and precautions for adults with COVID-19. 2021. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/duration-isolation.html. Accessed August 31, 2021.
30. Centers for Disease Control and Prevention. Investigative criteria for suspected cases of SARS-CoV-2 reinfection (ICR). 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/php/invest-criteria.html. Accessed August 31, 2021.
31. Kim AY, Gandhi RT. Reinfection with severe acute respiratory syndrome coronavirus 2: what goes around may come back around. *Clin Infect Dis*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7665341.
32. BNO News. COVID-19 reinfection tracker. 2020. Available at: https://bnonews.com/index.php/2020/08/covid-19-reinfection-tracker. Accessed August 31, 2021.
33. Datta SD, Talwar A, Lee JT. A proposed framework and timeline of the spectrum of disease due to SARS-CoV-2 infection: illness beyond acute infection and public health implications. *JAMA*. 2020;324(22):2251-2252. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33206133.
34. Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute COVID-19 in primary care. *BMJ*. 2020;370:m3026. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32784198.
35. Sudre CH, Murray B, Varsavsky T, et al. Attributes and predictors of Long-COVID: analysis of COVID cases and their symptoms collected by the COVID symptoms study app. *Nat Med*. 2021;27(4):626-631. Available at: https://pubmed.ncbi.nlm.nih.gov/33692530/.
36. Carfi A, Bernabei R, Landi F, Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent symptoms in patients after acute COVID-19. *JAMA*. 2020;324(6):603-605. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32644129.
37. Rawal G, Yadav S, Kumar R. Post-intensive care syndrome: an overview. *J Transl Int Med*. 2017;5(2):90-92. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28721340.
38. Tenforde MW, Kim SS, Lindsell CJ, et al. Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistate health care systems network—United States, March–June 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(30):993-998. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32730238.
39. Halpin SJ, McIvor C, Whyatt G, et al. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: a cross-sectional evaluation. *J Med Virol*. 2021;93(2):1013-1022. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32729939.
40. Cai X, Hu X, Ekumi IO, et al. Psychological distress and its correlates among COVID-19 survivors during early convalescence across age groups. *Am J Geriatr Psychiatry*. 2020;28(10):1030-1039. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32753338.

41. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet*. 2021;397(10270):220-232. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33428867.

42. Logue JK, Franko NM, MucCulloch DJ, et al. Sequelae in adults at 6 months after COVID-19 infection. *JAMA Netw Open*. 2021. Available at: https://pubmed.ncbi.nlm.nih.gov/33606031/.

43. Afshar Y, Gaw SL, Flaherman VJ, et al. Clinical presentation of coronavirus disease 2019 (COVID-19) in pregnant and recently pregnant people. *Obstet Gynecol*. 2020;136(6):1117-1125. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33027186.

44. Ludvigsson JF. Case report and systematic review suggest that children may experience similar long-term effects to adults after clinical COVID-19. *Acta Paediatr*. 2021 Mar;110(3):914-921. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33205450.

45. Buonsenso D, Munblit D, De Rose C, et al. Preliminary evidence on long COVID in children. *Acta Paediatr*. 2021;110(7):2208-2211. Available at: https://www.medrxiv.org/content/10.1101/2021.01.23.21250375v1.

46. Townsend L, Dyer AH, Jones K, et al. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. *PLoS One*. 2020;15(11):e0240784. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33166287.

47. Huang Y, Tan C, Wu J, et al. Impact of coronavirus disease 2019 on pulmonary function in early convalescence phase. *Respir Res*. 2020;21(1):163. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32600344.

48. Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2020;5(11):1265-1273. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32730619.

49. Huang L, Zhao P, Tang D, et al. Cardiac involvement in patients recovered from COVID-2019 identified using magnetic resonance imaging. *JACC Cardiovasc Imaging*. 2020;13(11):2330-2339. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32763118.

50. Mazza MG, De Lorenzo R, Conte C, et al. Anxiety and depression in COVID-19 survivors: role of inflammatory and clinical predictors. *Brain Behav Immun*. 2020;89:594-600. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32738287.

51. Lu Y, Li X, Geng D, et al. Cerebral micro-structural changes in COVID-19 patients—an MRI-based 3-month follow-up study. *EClinicalMedicine*. 2020;25:100484. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32838240.

52. Heneka MT, Golenbock D, Latz E, Morgan D, Brown R. Immediate and long-term consequences of COVID-19 infections for the development of neurological disease. *Alzheimers Res Ther*. 2020;12(1):69. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32498691.

53. Lechien JR, Chiesa-Estomba CM, Beckers E, et al. Prevalence and 6-month recovery of olfactory dysfunction: a multicentre study of 1363 COVID-19 patients. *J Intern Med*. 2021;290(2):451-461. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33403772.

54. Hampshire A, Trender W, Chamberlain SR, et al. Cognitive deficits in people who have recovered from COVID-19 relative to controls: an N = 84,285 online study. *medRxiv*. 2020;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2020.10.20.20215863v1.

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

Last Updated: March 24, 2022

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

The Food and Drug Administration's Emergency Use Authorizations provide a broad list of medical conditions or other factors as criteria for use of anti-SARS-CoV-2 agents as treatment or pre-exposure prophylaxis (PrEP). However, at times throughout the pandemic, increased cases of COVID-19 and the emergence of new variants of concern have resulted in logistical or supply constraints that made it impossible to offer the available therapy to all eligible patients. In those situations, prioritization of therapy for those who would have benefited the most became necessary. The purpose of this section is to provide guidance on which individuals might receive the greatest benefit from anti-SARS-CoV-2 therapeutics for treatment or prevention.

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

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

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

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

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

Patient Prioritization for Treatment

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

For a list of risk factors, see the Centers for Disease Control and Prevention (CDC) webpage Underlying

Medical Conditions Associated With Higher Risk for Severe COVID-19.

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

Patient Prioritization for Pre-Exposure Prophylaxis

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

Immunocompromising Conditions

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

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

- Patients who are within 1 year of receiving B cell–depleting therapies (e.g., rituximab, ocrelizumab, ofatumumab, alemtuzumab)
- Patients receiving Bruton's tyrosine kinase inhibitors
- Chimeric antigen receptor T cell recipients
- Post-hematopoietic cell transplant recipients who have chronic graft-versus-host disease or who are taking immunosuppressive medications for another indication
- Patients with hematologic malignancies who are on active therapy
- Lung transplant recipients

- Patients who are within 1 year of receiving a solid organ transplant (other than lung transplant)
- Solid organ transplant recipients who had recent treatment with T cell– or B cell–depleting agents for acute rejection
- Patients with severe combined immunodeficiencies
- Patients with untreated HIV who have CD4 T lymphocyte cell counts <50 cells/mm^3

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

Clinical Risk Factors

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

Although the data on risk factors for severe COVID-19 in children are limited, there is substantial overlap between risk factors in children and those identified in adults. Children who are 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]

References

1. Centers for Disease Control and Prevention. COVID-19 vaccines for moderately or severely immunocompromised people. 2022. Available at: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html. Accessed March 16, 2022.
2. Centers for Disease Control and Prevention. COVID-19 risks and vaccine information for older adults. 2021. Available at: https://www.cdc.gov/aging/covid19/covid19-older-adults.html. Accessed December 22, 2021.
3. Rosenthal N, Cao Z, Gundrum J, Sianis J, Safo S. Risk factors associated with in-hospital mortality in a U.S. national sample of patients with COVID-19. *JAMA Netw Open*. 2020;3(12):e2029058. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33301018.
4. Kompaniyets L, Agathis NT, Nelson JM, et al. Underlying medical conditions associated with severe COVID-19 illness among children. *JAMA Netw Open*. 2021;4(6):e2111182. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34097050.

Clinical Management Summary

Last Updated: April 1, 2022

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

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

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

PATIENT DISPOSITION	PANEL'S RECOMMENDATIONS
Does Not Require Hospitalization or Supplemental Oxygen	All patients should be offered symptomatic management **(AIII)**. For patients who are at high risk of progressing to severe COVID-19,[a] use 1 of the following treatment options: **Preferred Therapies** *Listed in order of preference:* • **Ritonavir-boosted nirmatrelvir (Paxlovid)[b,c] (AIIa)** • **Remdesivir[c,d] (BIIa)** **Alternative Therapies** *For use ONLY when neither of the preferred therapies are available, feasible to use, or clinically appropriate. Listed in alphabetical order:* • **Bebtelovimab[e] (CIII)** • **Molnupiravir[c,f] (CIIa)** For use **ONLY** in regions where the Omicron BA.2 subvariant is not the dominant subvariant and in situations where none of the preferred or alternative options are available, feasible to use, or clinically appropriate: • **Sotrovimab[g] (CIII)** The Panel **recommends against** the use of **dexamethasone** or **other systemic corticosteroids** in the absence of another indication **(AIII)**.[h]
Discharged From Hospital Inpatient Setting in Stable Condition and Does Not Require Supplemental Oxygen	The Panel **recommends against** continuing the use of **remdesivir (AIIa)**, **dexamethasone[h] (AIIa)**, or **baricitinib (AIIa)** after hospital discharge.
Discharged From Hospital Inpatient Setting and Requires Supplemental Oxygen *For those who are stable enough for discharge but who still require oxygen[i]*	There is insufficient evidence to recommend either for or against the continued use of remdesivir or dexamethasone.
Discharged From ED Despite New or Increasing Need for Supplemental Oxygen *When hospital resources are limited, inpatient admission is not possible, and close follow-up is ensured[j]*	The Panel recommends using **dexamethasone** 6 mg PO once daily for the duration of supplemental oxygen (dexamethasone use **should not** exceed 10 days) with careful monitoring for AEs **(BIII)**. Since remdesivir is recommended for patients with similar oxygen needs who are hospitalized,[k] clinicians may consider using it in this setting. Given that remdesivir requires IV infusions for up to 5 consecutive days, there may be logistical constraints to administering remdesivir in the outpatient setting.

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

[a] For a list of risk factors, see the CDC webpage Underlying Medical Conditions Associated With Higher Risk for Severe COVID-19 and the Patient Prioritization for Treatment section in Therapeutic Management of Nonhospitalized Adults With COVID-19.

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

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

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

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

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

[g] Sotrovimab is active against the Omicron BA.1 and BA.1.1 subvariants, but it has substantially decreased in vitro activity against the Omicron BA.2 subvariant. Visit the CDC COVID Data Tracker for information on the regional proportions of SARS-CoV-2 variants in the United States.

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

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

[j] Provide an advanced level of home care, including supplemental oxygen (whether patients are receiving oxygen for the first time or are increasing their baseline oxygen requirements), pulse .

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

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

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

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

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

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

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

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

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

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

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

[f] Contraindications for the use of therapeutic anticoagulation in patients with COVID-19 include platelet count <50 x 109/L, Hgb <8 g/dL, the need for dual antiplatelet therapy, bleeding within the last 30 days that required an ED visit or hospitalization, a history of a bleeding disorder, or an inherited or active acquired bleeding disorder. This list is based on the exclusion criteria from clinical trials; patients with these conditions have an increased risk of bleeding.

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

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

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

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

General Management of Nonhospitalized Patients With Acute COVID-19

Last Updated: December 16, 2021

Summary Recommendations
• Management of nonhospitalized patients with acute COVID-19 should include providing supportive care, considering the use of COVID-19-specific therapy for patients who have a high risk for disease progression, taking steps to reduce the risk of SARS-CoV-2 transmission (including isolating the patient), and advising patients on when to contact a health care provider and seek an in-person evaluation **(AIII)**. • When possible, patients with symptoms of COVID-19 should be triaged via telehealth visits to determine whether they require COVID-19-specific therapy and in-person care **(AIII)**. • Patients with dyspnea should be referred for an in-person evaluation by a health care provider and should be followed closely during the initial days after the onset of dyspnea to assess for worsening respiratory status **(AIII)**. • Management plans should be based on a patient's vital signs, physical exam findings, risk factors for progression to severe illness, and the availability of health care resources **(AIII)**. • See Therapeutic Management of Nonhospitalized Adults With COVID-19 for specific recommendations on using pharmacologic therapy in nonhospitalized patients.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional **Rating of Evidence:** I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

Introduction

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

This section focuses on the evaluation and management of:

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

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

Managing Patients With COVID-19 in an Ambulatory Care Setting

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

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

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

Assessing the Need for In-Person Evaluation

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

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

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

Clinical Considerations When Managing Patients in an Ambulatory Care Setting

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

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

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

Counseling Regarding the Need for Follow-Up

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

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

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

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

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

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

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

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

Managing Adults With COVID-19 Following Hospital Discharge

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

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

Considerations in Pregnancy

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

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

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

Considerations in Children

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

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

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

References

1. Centers for Medicare & Medicaid Services. CMS announces comprehensive strategy to enhance hospital capacity amid COVID-19 surge. 2020. Available at: https://www.cms.gov/newsroom/press-releases/cms-announces-comprehensive-strategy-enhance-hospital-capacity-amid-covid-19-surge. Accessed December 13, 2021.
2. Stokes EK, Zambrano LD, Anderson KN, et al. Coronavirus disease 2019 case surveillance—United States, January 22–May 30, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69. Available at: https://www.cdc.gov/mmwr/volumes/69/wr/pdfs/mm6924e2-H.pdf.
3. Centers for Disease Control and Prevention. Interim clinical guidance for management of patients with

confirmed coronavirus disease (COVID-19). 2021. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html. Accessed December 13, 2021.

4. Centers for Disease Control and Prevention. COVID-19: how to protect yourself & others. 2021. Available at: https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html. Accessed December 13, 2021.
5. Centers for Disease Control and Prevention. COVID-19: if you are sick or caring for someone. 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/. Accessed December 13, 2021.
6. Cheng A, Caruso D, McDougall C. Outpatient management of COVID-19: rapid evidence review. *Am Fam Physician*. 2020;102(8):478-486. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33064422.
7. Morrow-Howell N, Galucia N, Swinford E. Recovering from the COVID-19 pandemic: a focus on older adults. *J Aging Soc Policy*. 2020;32(4-5):526-535. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32336225.
8. Centers for Disease Control and Prevention. Coronavirus self-checker. 2021. Available at: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/coronavirus-self-checker.html. Accessed December 13, 2021.
9. Burkett E, Carpenter CR, Hullick C, Arendts G, Ouslander JG. It's time: delivering optimal emergency care of residents of aged care facilities in the era of COVID-19. *Emerg Med Australas*. 2021;33(1):131-137. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33131219.
10. Close RM, Stone MJ. Contact tracing for native americans in rural Arizona. *N Engl J Med*. 2020;383(3):e15. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32672426.
11. Centers for Disease Control and Prevention. COVID-19: what to do if you are sick. 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/steps-when-sick.html. Accessed December 13, 2021.
12. Centers for Disease Control and Prevention. COVID-19: isolate if you are sick. 2021. Available at: https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/isolation.html. Accessed December 13, 2021.
13. Cohen PA, Hall LE, John JN, Rapoport AB. The early natural history of SARS-CoV-2 infection: clinical observations from an urban, ambulatory COVID-19 clinic. *Mayo Clin Proc*. 2020;95(6):1124-1126. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32451119.
14. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061-1069. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32031570.
15. Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington state. *JAMA*. 2020;323(16):1612-1614. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32191259.
16. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020;8(5):475-481. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32105632.
17. Luks AM, Swenson ER. Pulse oximetry for monitoring patients with COVID-19 at home. Potential pitfalls and practical guidance. *Ann Am Thorac Soc*. 2020;17(9):1040-1046. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32521167.
18. Sjoding MW, Dickson RP, Iwashyna TJ, Gay SE, Valley TS. Racial bias in pulse oximetry measurement. *N Engl J Med*. 2020;383(25):2477-2478. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33326721.
19. Modi A, Kiroukas R, Scott JB. Accuracy of smartphone pulse oximeters in patients visiting an outpatient pulmonary function lab for a 6-minute walk test. *Respir Care*. 2019;64(Suppl 10). Available at: http://rc.rcjournal.com/content/64/Suppl_10/3238714.
20. Tarassenko L, Greenhalgh T. Question: should smartphone apps be used clinically as oximeters? Answer: no. 2020. Available at: https://www.cebm.net/covid-19/question-should-smartphone-apps-be-used-as-oximeters-answer-no/. Accessed December 13, 2021.

21. Jordan TB, Meyers CL, Schrading WA, Donnelly JP. The utility of iPhone oximetry apps: a comparison with standard pulse oximetry measurement in the emergency department. *Am J Emerg Med*. 2020;38(5):925-928. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31471076.
22. Meyer GS, Blanchfield BB, Bohmer RMJ, Mountford MB, Vanderwagen WC. Alternative care sites for the COVID-19 pandemic: the early U.S. and U.K. experience. *NEJM Catalyst*. 2020. Available at: https://catalyst.nejm.org/doi/full/10.1056/CAT.20.0224.
23. The American College of Obstetricians and Gynecologists. Outpatient assessment and management for pregnant women with suspected or confirmed novel coronavirus (COVID-19). 2020. Available at: https://www.smfm.org/covid19/. Accessed December 13, 2021.
24. The American College of Obstetricians and Gynecologists. COVID-19 FAQs for obstetrician-gynecologists, obstetrics. 2020. Available at: https://www.acog.org/clinical-information/physician-faqs/covid-19-faqs-for-ob-gyns-obstetrics. Accessed December 13, 2021.
25. Society for Maternal-Fetal Medicine. Management considerations for pregnant patients with COVID-19. 2020. Available at: https://s3.amazonaws.com/cdn.smfm.org/media/2336/SMFM_COVID_Management_of_COVID_pos_preg_patients_4-30-20_final.pdf.

Therapeutic Management of Nonhospitalized Adults With COVID-19

Last Updated: April 1, 2022

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

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

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

PATIENT DISPOSITION	PANEL'S RECOMMENDATIONS
Does Not Require Hospitalization or Supplemental Oxygen	All patients should be offered symptomatic management **(AIII)**. For patients who are at high risk of progressing to severe COVID-19,[a] use 1 of the following treatment options: **Preferred Therapies** *Listed in order of preference:* • **Ritonavir-boosted nirmatrelvir (Paxlovid)[b,c] (AIIa)** • **Remdesivir[c,d] (BIIa)** **Alternative Therapies** *For use ONLY when neither of the preferred therapies are available, feasible to use, or clinically appropriate. Listed in alphabetical order:* • **Bebtelovimab[e] (CIII)** • **Molnupiravir[c,f] (CIIa)** For use **ONLY** in regions where the Omicron BA.2 subvariant is not the dominant subvariant and in situations where none of the preferred or alternative options are available, feasible to use, or clinically appropriate: • **Sotrovimab[g] (CIII)** The Panel **recommends against** the use of **dexamethasone** or **other systemic corticosteroids** in the absence of another indication **(AIII)**.[h]
Discharged From Hospital Inpatient Setting in Stable Condition and Does Not Require Supplemental Oxygen	The Panel **recommends against** continuing the use of **remdesivir (AIIa)**, **dexamethasone[h] (AIIa)**, or **baricitinib (AIIa)** after hospital discharge.
Discharged From Hospital Inpatient Setting and Requires Supplemental Oxygen *For those who are stable enough for discharge but who still require oxygen[i]*	There is insufficient evidence to recommend either for or against the continued use of remdesivir or dexamethasone.
Discharged From ED Despite New or Increasing Need for Supplemental Oxygen *When hospital resources are limited, inpatient admission is not possible, and close follow-up is ensured[j]*	The Panel recommends using **dexamethasone** 6 mg PO once daily for the duration of supplemental oxygen (dexamethasone use **should not** exceed 10 days) with careful monitoring for AEs **(BIII)**. Since remdesivir is recommended for patients with similar oxygen needs who are hospitalized,[k] clinicians may consider using it in this setting. Given that remdesivir requires IV infusions for up to 5 consecutive days, there may be logistical constraints to administering remdesivir in the outpatient setting.

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

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

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

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

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

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

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

[g] Sotrovimab is active against the Omicron BA.1 and BA.1.1 subvariants, but it has substantially decreased in vitro activity against the Omicron BA.2 subvariant. Visit the CDC COVID Data Tracker for information on the regional proportions of SARS-CoV-2 variants in the United States.

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

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

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

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

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

Patient Prioritization for Treatment

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

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

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

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

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

Immunocompromising Conditions

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

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

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

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

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

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

Drug Name	Dosing Regimen	Time From Symptom Onset[a]
Ritonavir-Boosted Nirmatrelvir (Paxlovid), continued	**eGFR <30 mL/min:** **• Not recommended** **Severe Hepatic Impairment (Child-Pugh Class C):** **• Not recommended**	≤5 days
Remdesivir	RDV 200 mg IV on Day 1, followed by RDV 100 mg IV once daily on Days 2 and 3.[b,c] Each infusion should be administered over 30–120 minutes. Patients should be observed for ≥1 hour after infusion as clinically appropriate.	≤7 days
Bebtelovimab	BEB 175 mg as a single IV injection, administered over ≥30 seconds. Patients should be observed for ≥1 hour after injection.	≤7 days
Molnupiravir	Molnupiravir 800 mg PO twice daily for 5 days	≤5 days
Sotrovimab	SOT 500 mg as a single IV infusion administered over 30 minutes. Patients should be observed for ≥1 hour after infusion.	≤7 days

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

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

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

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

Symptom Management

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

Rationale for the Use of Specific Agents Listed in Figure 1

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

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

The Panel recommends ritonavir-boosted nirmatrelvir or remdesivir as preferred therapy options because

Phase 3 randomized placebo-controlled trials have reported high clinical efficacies for these agents in patients with COVID-19.[3,4] The Panel favors the use of ritonavir-boosted nirmatrelvir in most high-risk, nonhospitalized patients with mild to moderate COVID-19. If ritonavir-boosted nirmatrelvir is not available or cannot be used because of drug interactions, the Panel recommends using remdesivir as the second option.

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

Sotrovimab, which is active against the Omicron BA.1 and BA.1.1 subvariants, has substantially decreased in vitro activity against the Omicron BA.2 subvariant that is rapidly becoming the dominant subvariant in the United States.[5-7] In the recently updated EUA, the FDA states that sotrovimab is not authorized for use in geographic regions where infection is likely to have been caused by a nonsusceptible SARS-CoV-2 variant.[6] Distribution of sotrovimab was recently paused in some regions of the United States.[8] As a result, the Panel recommends using sotrovimab only in regions where the Omicron BA.2 subvariant is not the dominant subvariant and only in cases where none of the preferred or alternative treatment options are available, feasible to use, or clinically appropriate.

There are currently no clinical trial data that directly compare the clinical efficacy of these 5 therapies, and there are no data on the use of combinations of antiviral agents and/or anti-SARS-CoV-2 mAbs for the treatment of COVID-19. The rationale for each of the Panel's recommendations is discussed below.

Ritonavir-Boosted Nirmatrelvir (Paxlovid)

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

Recommendations

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

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

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

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

Remdesivir

Remdesivir is currently approved by the FDA for use in hospitalized patients with COVID-19 and in nonhospitalized patients with mild to moderate COVID-19 who are at high risk of disease progression. Remdesivir has been studied in nonhospitalized patients with mild to moderate COVID-19 who were at high risk of progressing to severe disease. The PINETREE trial showed that 3 consecutive days of intravenous (IV) remdesivir resulted in an 87% relative reduction in the risk of hospitalization or death compared to placebo.[4] Remdesivir is expected to be active against the Omicron VOC, although in vitro and in vivo data are currently limited.[14] See the Remdesivir section for more details.

Recommendations

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

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

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

Bebtelovimab

Bebtelovimab is a recombinant neutralizing human mAb that binds to the spike protein of SARS-CoV-2. Based on in vitro data, bebtelovimab is expected to have activity against a broad range of SARS-CoV-2 variants, including the Omicron VOC and its BA.1, BA.1.1, and BA.2 subvariants.[7,17] However, to date, the clinical trial data for bebtelovimab come from a single Phase 2 randomized placebo-controlled trial in patients with COVID-19 who were at low risk of progressing to severe disease. The trial showed no unexpected safety events, and patients who received bebtelovimab had more rapid viral decay than those who received the placebo.

Recommendations

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

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

Molnupiravir

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

Molnupiravir has potent antiviral activity against SARS-CoV-2.[18] As a mutagenic ribonucleoside antiviral agent, there is a theoretical risk that molnupiravir will be metabolized by the human host cell and incorporated into the host DNA, leading to mutations. Molnupiravir has been evaluated in 2 in vivo rodent mutagenicity assays. One study produced equivocal results; in the other study, there was no evidence for mutagenicity. The FDA concluded that, based on the available genotoxicity data and the 5-day duration of treatment, molnupiravir has a low risk for genotoxicity.[20] In addition, there have been concerns about the potential effects of molnupiravir on SARS-CoV-2 mutation rates; the FDA is requiring the manufacturer to establish a process to monitor genomic databases for the emergence of SARS-CoV-2 variants.

Molnupiravir is expected to be active against the Omicron VOC, although in vitro and in vivo data are currently limited.[14]

Recommendation

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

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

placebo in nonhospitalized patients with COVID-19.[13,20] Even though the different treatment options have not been directly compared in clinical trials, the Panel recommends using molnupiravir only when ritonavir-boosted nirmatrelvir and remdesivir are not available or cannot be used, because molnupiravir has lower efficacy than the other options **(CIIa)**.

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

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

Sotrovimab

Laboratory studies indicate that sotrovimab remains active against the Omicron BA.1 and BA.1.1 subvariants,[21] but it has substantially decreased activity against the Omicron BA.2 subvariant that is rapidly becoming the dominant subvariant in the United States.[5-7]

Recommendations

- The Panel recommends using a single IV infusion of **sotrovimab 500 mg** in those aged ≥12 years and weighing ≥40 kg, but only in regions where the Omicron BA.2 subvariant is not the dominant variant and only when none of the preferred or alternative treatment options are available, feasible to use, or clinically appropriate; treatment should be administered as soon as possible and within 7 days of symptom onset **(CIII)**. Clinicians should visit the CDC COVID Data Tracker for up-to-date information on the regional proportions of SARS-CoV-2 variants in the United States.
- Sotrovimab 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.

The data that support the EUA for sotrovimab come from the Phase 3 COMET-ICE trial, which included outpatients aged ≥18 years with mild to moderate COVID-19 who were at high risk for progressing to severe COVID-19 and were within 5 days of symptom onset.[22] The primary endpoint of the study was the proportion of participants who were hospitalized for ≥24 hours or who died from any cause by Day 29. Endpoint events occurred in 6 of 528 participants (1%) in the sotrovimab arm and in 30 of 529 participants (6%) in the placebo arm ($P = 0.002$), resulting in a -4.53% absolute difference in the risk of hospitalization or death among those who received sotrovimab. The adjusted relative risk of hospitalization or death for those who received sotrovimab was 0.21 (95% CI, 0.09–0.50).[6,22] Although the study only enrolled participants who were within 5 days of symptom onset, the EUA allows sotrovimab to be used in people who are within 7 days of symptom onset.

Dexamethasone

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

In the RECOVERY trial, dexamethasone was shown to reduce mortality in hospitalized patients with COVID-19 who required supplemental oxygen.[23] Nonhospitalized patients who did not require supplemental oxygen were not included in this trial. The Panel **recommends against** the use of **dexamethasone** or **other systemic glucocorticoids** in this population, as there are no clinical trial data to support their use **(AIII)**.

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

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

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

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

- The Panel **recommends against** the use of **chloroquine** or **hydroxychloroquine** with or without **azithromycin (AI)**, **lopinavir/ritonavir**, and **other HIV protease inhibitors (AIII)** for the outpatient treatment of COVID-19.
- The Panel **recommends against** the use of **antibacterial therapy** (e.g., **azithromycin**, **doxycycline**) for the outpatient treatment of COVID-19 in the absence of another indication **(AIII)**.
- Other agents have undergone or are currently undergoing investigation in the outpatient setting. For more information, please refer to the sections of the Guidelines that address:
  - Antiviral agents, such as ivermectin and nitazoxanide
  - Convalescent plasma
  - Immunomodulators, such as colchicine, fluvoxamine, and inhaled corticosteroids
  - Supplements, such as vitamin C, vitamin D, and zinc
- The Panel **recommends against** the use of **anticoagulants** and **antiplatelet therapy** for the prevention of venous thromboembolism or arterial thrombosis unless the patient has other indications for the therapy or is participating in a clinical trial **(AIIa)**. For more information, see Antithrombotic Therapy in Patients With COVID-19.
- Health care providers should provide information about ongoing clinical trials of investigational

therapies to eligible outpatients with COVID-19 so they can make informed decisions about participation **(AIII)**.

Concomitant Medication Management

In general, a patient's usual medication and/or supplement regimen should be continued after the diagnosis of COVID-19 (see Considerations for Using Concomitant Medications in Patients With COVID-19). **Angiotensin-converting enzyme inhibitors**, **statin therapy**, **nonsteroidal anti-inflammatory drugs**, and **oral**, **inhaled**, and **intranasal corticosteroids** that are prescribed for comorbid conditions should be continued as directed **(AIII)**. Patients should be advised to avoid the use of nebulized medications in the presence of others to avoid potential aerosolization of SARS-CoV-2.[24] In patients with HIV, antiretroviral therapy should not be switched or adjusted for the purpose of preventing or treating SARS-CoV-2 infection **(AIII)**. For more information, see Special Considerations in People With HIV.

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

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

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

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

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

References

1. Caputo ND, Strayer RJ, Levitan R. Early self-proning in awake, non-intubated patients in the emergency department: a single ED's experience during the COVID-19 pandemic. *Acad Emerg Med*. 2020;27(5):375-378. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32320506.
2. National Institute for Health Care Excellence (NICE) in collaboration with NHS England and NHS Improvement. Managing COVID-19 symptoms (including at the end of life) in the community: summary of NICE guidelines. *BMJ*. 2020;369:m1461. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32312715.
3. Hammond J, Leister-Tebbe H, Gardner A, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with COVID-19. *N Engl J Med*. 2022;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35172054.

4. Gottlieb RL, Vaca CE, Paredes R, et al. Early remdesivir to prevent progression to severe COVID-19 in outpatients. *N Engl J Med*. 2022;386(4):305-315. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34937145.
5. Takashita E, Kinoshita N, Yamayoshi S, et al. Efficacy of antiviral agents against the SARS-CoV-2 Omicron subvariant BA.2. *N Engl J Med*. 2022;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35263535.
6. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of sotrovimab. 2022;Published online ahead of print. Available at: https://www.fda.gov/media/149534/download.
7. Iketani S, Liu L, Guo Y, et al. Antibody evasion properties of SARS-CoV-2 Omicron sublineages. *Nature*. 2022;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35240676.
8. Public Health Emergency. Sotrovimab. 2022. Available at: https://www.phe.gov/emergency/events/COVID19/investigation-MCM/Sotrovimab/Pages/default.aspx. Accessed March 31, 2022.
9. Pillaiyar T, Manickam M, Namasivayam V, Hayashi Y, Jung SH. An overview of severe acute respiratory syndrome-coronavirus (SARS-CoV) 3CL protease inhibitors: peptidomimetics and small molecule chemotherapy. *J Med Chem*. 2016;59(14):6595-6628. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26878082.
10. Owen DR, Allerton CMN, Anderson AS, et al. An oral SARS-CoV-2 M(pro) inhibitor clinical candidate for the treatment of COVID-19. *Science*. 2021;374(6575):1586-1593. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34726479.
11. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for Paxlovid. 2022. Available at: https://www.fda.gov/media/155050/download.
12. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Early treatment for COVID-19 with SARS-CoV-2 neutralizing antibody sotrovimab. *N Engl J Med*. 2021;385(21):1941-1950. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34706189.
13. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for oral treatment of COVID-19 in nonhospitalized patients. *N Engl J Med*. 2022;386(6):509-520. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34914868.
14. Vangeel L, Chiu W, De Jonghe S, et al. Remdesivir, molnupiravir and nirmatrelvir remain active against SARS-CoV-2 Omicron and other variants of concern. *Antiviral Res*. 2022;198:105252. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35085683.
15. Greasley SE, Noell S, Plotnikova O, et al. Structural basis for nirmatrelvir in vitro efficacy against the Omicron variant of SARS-CoV-2. *bioRxiv*. 2022;Preprint. Available at: https://www.biorxiv.org/content/10.1101/2022.01.17.476556v1.
16. Rai DK, Yurgelonis I, McMonagle P, et al. Nirmatrelvir, an orally active Mpro inhibitor, is a potent inhibitor of SARS-CoV-2 variants of concern. *bioRxiv*. 2022;Preprint. Available at: https://www.biorxiv.org/content/10.1101/2022.01.17.476644v1.
17. Westendorf K, Zentelis S, Wang L, et al. LY-CoV1404 (bebtelovimab) potently neutralizes SARS-CoV-2 variants. *bioRxiv*. 2022;Preprint. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33972947.
18. Zhou S, Hill CS, Sarkar S, et al. Beta-d-N4-hydroxycytidine inhibits SARS-CoV-2 through lethal mutagenesis but is also mutagenic to mammalian cells. *J Infect Dis*. 2021;224(3):415-419. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33961695.
19. Kabinger F, Stiller C, Schmitzova J, et al. Mechanism of molnupiravir-induced SARS-CoV-2 mutagenesis. *Nat Struct Mol Biol*. 2021;28(9):740-746. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34381216.
20. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for molnupiravir. 2022. Available at: https://www.fda.gov/media/155054/download.
21. Cathcart AL, Havenar-Daughton C, Lempp FA, et al. The dual function monoclonal antibodies VIR-7831 and VIR-7832 demonstrate potent in vitro and in vivo activity against SARS-CoV-2. *bioRxiv*. 2021;Preprint.

Available at: https://www.biorxiv.org/content/10.1101/2021.03.09.434607v10.

22. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Effect of sotrovimab on hospitalization or death among high-risk patients with mild to moderate COVID-19: a randomized clinical trial. *JAMA*. 2022. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35285853.
23. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with COVID-19. *N Engl J Med*. 2021;384(8):693-704. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32678530.
24. Cazzola M, Ora J, Bianco A, Rogliani P, Matera MG. Guidance on nebulization during the current COVID-19 pandemic. *Respir Med*. 2021;176:106236. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33248363.

Therapeutic Management of Hospitalized Adults With COVID-19

Last Updated: February 24, 2022

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Introduction

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

Patients Who Do Not Require Supplemental Oxygen

Recommendations

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

Rationale for Recommending Against the Use of Dexamethasone or Other Corticosteroids

In the RECOVERY trial, a multicenter, open-label trial in the United Kingdom, hospitalized patients with COVID-19 were randomized to receive dexamethasone plus standard of care or standard of care alone (control arm).[1] No survival benefit for dexamethasone was observed among the patients who did not require supplemental oxygen at enrollment: 17.8% of patients in the dexamethasone arm and 14% in the control arm died within 28 days of enrollment (rate ratio 1.19; 95% CI, 0.91–1.55). See Table 4a for additional information.

Based on these data, the Panel **recommends against** the use of **dexamethasone (AIIa)** or **other corticosteroids (AIII)** for the treatment of COVID-19 in hospitalized patients who do not require supplemental oxygen, unless the patient has another indication for corticosteroid therapy.

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

ACTT-1 was a multinational randomized controlled trial that compared intravenous (IV) remdesivir to placebo in hospitalized patients with COVID-19. Remdesivir showed no significant benefit in patients with mild to moderate disease, which was defined as oxygen saturation >94% on room air or a respiratory rate <24 breaths/min without supplemental oxygen (rate ratio for recovery 1.29; 95% CI, 0.91–1.83); however, there were only 138 patients in this subgroup.[2]

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

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

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

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

Patients Who Require Supplemental Oxygen

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

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

Recommendations

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

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

Rationale for the Use of Remdesivir

In the ACTT-1 trial, remdesivir was associated with improved time to recovery in the 435 patients who required oxygen supplementation but not high-flow oxygen, NIV, or mechanical ventilation (7 days for remdesivir vs. 9 days for placebo; recovery rate ratio 1.45; 95% CI, 1.18–1.79). Fewer patients in the remdesivir arm than in the placebo arm progressed to requiring high-flow oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) (17% vs. 24%). In a post hoc analysis of deaths by Day 29, remdesivir appeared to confer a substantial survival benefit in this subgroup (HR for death 0.30; 95% CI, 0.14–0.64).[2]

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

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

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

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

Rationale for the Use of Remdesivir Plus Dexamethasone

The safety and efficacy of using a combination of remdesivir and corticosteroids have primarily been evaluated in observational studies. Some of these studies have suggested that there is a clinical benefit of using remdesivir plus dexamethasone.[8-10] Remdesivir plus dexamethasone has not been directly compared to dexamethasone alone in a large randomized clinical trial. Patients with severe COVID-19 may develop a systemic inflammatory response that leads to multiple organ dysfunction syndrome. The potent anti-inflammatory effects of corticosteroids might prevent or mitigate these hyperinflammatory effects. Thus, the combination of an antiviral agent, such as remdesivir, with an anti-inflammatory agent, such as dexamethasone, may treat the viral infection and dampen the potentially injurious inflammatory response that is a consequence of the infection.

Based on the theoretical combined benefit of antiviral and anti-inflammatory therapies, the Panel recommends the combination of **dexamethasone plus remdesivir** as a treatment option for patients who require supplemental oxygen **(BIIb)**, despite important limitations of observational data.

Rationale for the Use of Dexamethasone

In the RECOVERY trial, treatment with dexamethasone conferred a survival benefit among patients who required supplemental oxygen at enrollment. Fewer patients in the dexamethasone arm than in the standard of care arm died within 28 days of enrollment (23.3% vs. 26.2%; rate ratio 0.82; 95% CI, 0.72–0.94).[1] However, the amount of supplemental oxygen that patients were receiving and the proportions of patients who required oxygen through a high-flow device or NIV were not reported. It is possible that the benefit of dexamethasone was greatest in those who required more respiratory support. It should be noted that <0.1% of patients in the RECOVERY trial received concomitant remdesivir. For more information, see Corticosteroids.

Some experts prefer not to use dexamethasone monotherapy in patients who require supplemental oxygen because of the theoretical concern that corticosteroids might slow viral clearance when administered without an antiviral drug. Corticosteroids have been associated with delayed viral clearance and/or worse clinical outcomes in patients with other viral respiratory infections.[11-13] Some studies have suggested that corticosteroids slow SARS-CoV-2 clearance, but the results to date are inconclusive.[14-18]

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

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

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

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

Additional Considerations

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

Rationale for Using a Therapeutic Dose of Heparin in Certain Patients

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

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

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

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

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

Recommendations

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

Additional Considerations

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

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

Rationale for the Use of Dexamethasone

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

Rationale for the Use of Remdesivir Plus Dexamethasone

The safety and efficacy of using a combination of remdesivir and corticosteroids have primarily been evaluated in observational studies. Some of these studies have suggested that there is a clinical benefit of using remdesivir plus dexamethasone.[8-10] Remdesivir plus dexamethasone has not been directly compared to dexamethasone alone in a large randomized clinical trial. Patients with severe COVID-19 may develop a systemic inflammatory response that leads to multiple organ dysfunction syndrome. The potent anti-inflammatory effects of corticosteroids might prevent or mitigate these hyperinflammatory effects. Thus, the combination of an antiviral agent, such as remdesivir, with an anti-inflammatory agent, such as dexamethasone, may treat the viral infection and dampen the potentially injurious inflammatory response that is a consequence of the infection. Based on the theoretical combined benefit of antiviral and anti-inflammatory therapies, the Panel recommends the combination of **dexamethasone plus remdesivir** as a treatment option for patients who require high-flow oxygen or NIV **(BIIb)**, despite the limitations of observational data.

Rationale for Not Recommending Remdesivir Monotherapy

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

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

Rationale for Adding a Second Immunomodulatory Drug to Dexamethasone in Certain Hospitalized Patients

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

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

both studies received corticosteroids.

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

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

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

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

Additional Considerations

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

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

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

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

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

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

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

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

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

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

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

Rationale for the Use of Prophylactic Doses of Heparin

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

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

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

Patients Who Require Mechanical Ventilation or Extracorporeal Membrane Oxygenation

Recommendations

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

Additional Considerations

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

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

Rationale for the Use of Dexamethasone Monotherapy

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

Dexamethasone reduces mortality in critically ill patients with COVID-19 according to a meta-analysis that aggregated 7 randomized trials and included data on 1,703 critically ill patients.[31] The largest trial in the meta-analysis was the RECOVERY trial, whose subgroup of mechanically ventilated patients was included.[1] For details about the meta-analysis and the RECOVERY trial, see Corticosteroids and Table 4a. Because the benefits of dexamethasone outweigh the potential harms, the Panel recommends using **dexamethasone** in hospitalized patients with COVID-19 who require mechanical ventilation or ECMO **(AI)**.

Considerations Related to the Use of Dexamethasone Plus Remdesivir Combination Therapy

Dexamethasone plus remdesivir combination therapy has not been evaluated in controlled studies; therefore, there is insufficient information to make a recommendation either for or against the use of this combination therapy. However, there is a theoretical reason to administer dexamethasone plus remdesivir to patients who have recently been intubated. Antiviral therapy may prevent a steroid-related delay in viral clearance. This delay has been reported in the setting of other viral infections.[11,12]

Some studies have suggested that corticosteroids slow SARS-CoV-2 clearance, but the studies to date are not definitive. For example, an observational study in patients with nonsevere COVID-19 suggested that viral clearance was delayed in those who received corticosteroids,[32] whereas a more recent study in patients with moderate to severe COVID-19 found no relationship between the use of corticosteroids and the rate of viral clearance.[18] Given the conflicting results from observational studies and the lack of clinical trial data, some Panel members would coadminister **dexamethasone** and **remdesivir** in patients who have recently been placed on mechanical ventilation **(CIII)** until more conclusive evidence becomes available, based on their concerns about delayed viral clearance in patients who received corticosteroids. Other Panel members would not coadminister dexamethasone and remdesivir due to uncertainties about the benefit of using remdesivir in critically ill patients.

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

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

Rationale for Recommending Against the Use of Remdesivir Monotherapy

A clear benefit of remdesivir monotherapy has not been demonstrated in patients who require mechanical ventilation or ECMO. In the ACTT-1 trial, remdesivir did not improve the recovery rate in this subgroup of patients (recovery rate ratio 0.98; 95% CI, 0.70–1.36), and in a post hoc analysis of deaths by Day 29, remdesivir did not improve survival in this subgroup (HR 1.13; 95% CI, 0.67–1.89).[2] In the Solidarity trial, there was a trend toward increased mortality among patients who received mechanical ventilation and were randomized to receive remdesivir rather than standard of care (rate ratio 1.27; 95% CI, 0.99–1.62).[4] Taken together, these results do not demonstrate a clear benefit of remdesivir in critically ill patients.

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

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

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

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

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

Rationale for the Use of Prophylactic Doses of Heparin

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

References

1. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with COVID-19. *N Engl J Med*. 2021;384(8):693-704. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32678530.
2. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of COVID-19 - final report. *N Engl J Med*. 2020;383(19):1813-1826. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32445440.
3. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. *JAMA*. 2020;324(11):1048-1057. Available at:

https://www.ncbi.nlm.nih.gov/pubmed/32821939.

4. WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed antiviral drugs for COVID-19—interim WHO Solidarity trial results. *N Engl J Med*. 2021;384(6):497-511. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33264556.
5. Hill JA, Paredes R, Vaca C, et al. Remdesivir for the treatment of high-risk non-hospitalized individuals with COVID-19: a randomized, double-blind, placebo-controlled trial. Presented at IDWeek. 2021. Virtual.
6. Ader F, Bouscambert-Duchamp M, Hites M, et al. Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a Phase 3, randomised, controlled, open-label trial. *Lancet Infect Dis*. 2022;22(2):209-221. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34534511.
7. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 days in patients with severe COVID-19. *N Engl J Med*. 2020;383(19):1827-1837. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32459919.
8. Wong CKH, Lau KTK, Au ICH, et al. Optimal timing of remdesivir initiation in hospitalized COVID-19 patients administered with dexamethasone. *Clin Infect Dis*. 2021;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34420051.
9. Benfield T, Bodilsen J, Brieghel C, et al. Improved survival among hospitalized patients with coronavirus disease 2019 (COVID-19) treated with remdesivir and dexamethasone. A nationwide population-based cohort study. *Clin Infect Dis*. 2021;73(11):2031-2036. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34111274.
10. Mozaffari E, Chandak A, Zhang Z, et al. Remdesivir treatment in hospitalized patients with COVID-19: a comparative analysis of in-hospital all-cause mortality in a large multi-center observational cohort. *Clin Infect Dis*. 2021;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34596223.
11. Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid therapy for critically ill patients with Middle East respiratory syndrome. *Am J Respir Crit Care Med*. 2018;197(6):757-767. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29161116.
12. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Med*. 2006;3(9):e343. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16968120.
13. Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, Lim WS. Corticosteroids as adjunctive therapy in the treatment of influenza. *Cochrane Database Syst Rev*. 2016;3:CD010406. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26950335.
14. Chen Y, Li L. Influence of corticosteroid dose on viral shedding duration in patients with COVID-19. *Clin Infect Dis*. 2021;72(7):1298-1300. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32588884.
15. Li S, Hu Z, Song X. High-dose but not low-dose corticosteroids potentially delay viral shedding of patients with COVID-19. *Clin Infect Dis*. 2021;72(7):1297-1298. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32588877.
16. Ding C, Feng X, Chen Y, et al. Effect of corticosteroid therapy on the duration of SARS-CoV-2 clearance in patients with mild COVID-19: a retrospective cohort study. *Infect Dis Ther*. 2020;9(4):943-952. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32986226.
17. Liu J, Zhang S, Dong X, et al. Corticosteroid treatment in severe COVID-19 patients with acute respiratory distress syndrome. *J Clin Invest*. 2020;130(12):6417-6428. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33141117.
18. Spagnuolo V, Guffanti M, Galli L, et al. Viral clearance after early corticosteroid treatment in patients with moderate or severe COVID-19. *Sci Rep*. 2020;10(1):21291. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33277573.
19. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. 2021;397(10285):1637-1645. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33933206.
20. Marconi VC, Ramanan AV, de Bono S, et al. Efficacy and safety of baricitinib for the treatment of hospitalised

adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled Phase 3 trial. *Lancet Respir Med*. 2021;9(12):1407-1418. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34480861.

21. Guimaraes PO, Quirk D, Furtado RH, et al. Tofacitinib in patients hospitalized with COVID-19 pneumonia. *N Engl J Med*. 2021;385(5):406-415. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34133856.
22. Lier AJ, Tuan JJ, Davis MW, et al. Case report: disseminated strongyloidiasis in a patient with COVID-19. *Am J Trop Med Hyg*. 2020;103(4):1590-1592. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32830642.
23. Marchese V, Crosato V, Gulletta M, et al. Strongyloides infection manifested during immunosuppressive therapy for SARS-CoV-2 pneumonia. *Infection*. 2021;49(3):539-542. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32910321.
24. ATTACC Investigators, ACTIV-4a Investigators, REMAP-CAP Investigators, et al. Therapeutic anticoagulation with heparin in noncritically ill patients with COVID-19. *N Engl J Med*. 2021;385(9):790-802. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34351721.
25. Sholzberg M, Tang GH, Rahhal H, et al. Effectiveness of therapeutic heparin versus prophylactic heparin on death, mechanical ventilation, or intensive care unit admission in moderately ill patients with COVID-19 admitted to hospital: RAPID randomised clinical trial. *BMJ*. 2021;375:n2400. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34649864.
26. Spyropoulos AC, Goldin M, Giannis D, et al. Efficacy and safety of therapeutic-dose heparin vs standard prophylactic or intermediate-dose heparins for thromboprophylaxis in high-risk hospitalized patients with COVID-19: the HEP-COVID randomized clinical trial. *JAMA Intern Med*. 2021;181(12):1612-1620. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34617959.
27. REMAP-CAP Investigators, Gordon AC, Mouncey PR, et al. Interleukin-6 receptor antagonists in critically ill patients with COVID-19. *N Engl J Med*. 2021;384(16):1491-1502. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33631065.
28. The REMAP-CAP Investigators, Derde LPG. Effectiveness of tocilizumab, sarilumab, and anakinra for critically ill patients with COVID-19: the REMAP-CAP COVID-19 immune modulation therapy domain randomized clinical trial. *medRxiv*. 2021;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.06.18.21259133v2.
29. Inspiration Investigators, Sadeghipour P, Talasaz AH, et al. Effect of intermediate-dose vs standard-dose prophylactic anticoagulation on thrombotic events, extracorporeal membrane oxygenation treatment, or mortality among patients with COVID-19 admitted to the intensive care unit: the INSPIRATION randomized clinical trial. *JAMA*. 2021;325(16):1620-1630. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33734299.
30. The REMAP-CAP, ACTIV-4a, ATTACC Investigators, Zarychanski R. Therapeutic anticoagulation in critically ill patients with COVID-19—Preliminary Report. *medRxiv*. 2021;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.03.10.21252749v1.
31. WHO Rapid Evidence Appraisal for COVID-19 Therapies Working Group, Sterne JAC, Murthy S, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA*. 2020;324(13):1330-1341. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32876694.
32. Li Q, Li W, Jin Y, et al. Efficacy evaluation of early, low-dose, short-term corticosteroids in adults hospitalized with non-severe COVID-19 pneumonia: a retrospective cohort study. *Infect Dis Ther*. 2020;9(4):823-836. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32880102.
33. Ely EW, Ramanan AV, Kartman CE, et al. Baricitinib plus standard of care for hospitalised adults with COVID-19 on invasive mechanical ventilation or extracorporeal membrane oxygenation: results of a randomised, placebo-controlled trial. *medRxiv*. 2021;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.10.11.21263897v2.

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

Last Updated: February 24, 2022

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

Multisystem Inflammatory Syndrome in Adults

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

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

PANEL'S RECOMMENDATIONS

MIS-C

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

Initial Immunomodulatory Therapy:

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

Intensification Immunomodulatory Therapy:

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

Antithrombotic Treatment:

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

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

[a] 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 A. Dosing Regimens for the Drugs Recommended for the Treatment of MIS-C

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

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

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]

References

1. Centers for Disease Control and Prevention. Information for healthcare providers about multisystem inflammatory syndrome in children (MIS-C). 2021. Available at: https://www.cdc.gov/mis/mis-c/hcp/index.html. Accessed February 7, 2022.
2. Centers for Disease Control and Prevention. Multisystem inflammatory syndrome in adults (MIS-A) case definition information for healthcare providers. 2021. Available at: https://www.cdc.gov/mis/mis-a/hcp.html. Accessed February 7, 2022.
3. Morris SB, Schwartz NG, Patel P, et al. Case series of multisystem inflammatory syndrome in adults associated with SARS-CoV-2 infection—United Kingdom and United States, March–August 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(40):1450-1456. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33031361.
4. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet*. 2020;395(10239):1771-1778. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32410760.
5. Belhadjer Z, Auriau J, Meot M, et al. Addition of corticosteroids to immunoglobulins is associated with recovery of cardiac function in multi-inflammatory syndrome in children. *Circulation*. 2020;142(23):2282-2284. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33112651.
6. Toubiana J, Poirault C, Corsia A, et al. Kawasaki-like multisystem inflammatory syndrome in children during the COVID-19 pandemic in Paris, France: prospective observational study. *BMJ*. 2020;369:m2094. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32493739.

7. Whittaker E, Bamford A, Kenny J, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. *JAMA*. 2020;324(3):259-269. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32511692.
8. Pouletty M, Borocco C, Ouldali N, et al. Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (Kawa-COVID-19): a multicentre cohort. *Ann Rheum Dis*. 2020;79(8):999-1006. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32527868.
9. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. *N Engl J Med*. 2020;383(4):334-346. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32598831.
10. Dufort EM, Koumans EH, Chow EJ, et al. Multisystem inflammatory syndrome in children in New York State. *N Engl J Med*. 2020;383(4):347-358. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32598830.
11. Lee PY, Day-Lewis M, Henderson LA, et al. Distinct clinical and immunological features of SARS-CoV-2-induced multisystem inflammatory syndrome in children. *J Clin Inves*t. 2020;130(11):5942-5950. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32701511.
12. Feldstein LR, Tenforde MW, Friedman KG, et al. Characteristics and outcomes of US children and adolescents with multisystem inflammatory syndrome in children (MIS-C) compared with severe acute COVID-19. *JAMA*. 2021;325(11):1074-1087. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33625505.
13. American College of Rheumatology. Clinical guidance for pediatric patients with multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 and hyperinflammation in COVID-19. 2022. Available at: https://www.rheumatology.org/Portals/0/Files/ACR-COVID-19-Clinical-Guidance-Summary-MIS-C-Hyperinflammation.pdf.
14. Ouldali N, Toubiana J, Antona D, et al. Association of intravenous immunoglobulins plus methylprednisolone vs immunoglobulins alone with course of fever in multisystem inflammatory syndrome in children. *JAMA*. 2021;325(9):855-864. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33523115.
15. Son MBF, Murray N, Friedman K, et al. Multisystem inflammatory syndrome in children—initial therapy and outcomes. *N Engl J Med*. 2021;385(1):23-34. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34133855.
16. McArdle AJ, Vito O, Patel H, et al. Treatment of multisystem inflammatory syndrome in children. *N Engl J Med*. 2021;385(1):11-22. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34133854.
17. Jonat B, Gorelik M, Boneparth A, et al. Multisystem inflammatory syndrome in children associated with coronavirus disease 2019 in a children's hospital in New York City: patient characteristics and an institutional protocol for evaluation, management, and follow-up. *Pediatr Crit Care Med*. 2021;22(3):e178-e191. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33003176.
18. Newburger JW, Takahashi M, Burns JC, et al. The treatment of Kawasaki syndrome with intravenous gamma globulin. *N Engl J Med*. 1986;315(6):341-347. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2426590.
19. Furusho K, Kamiya T, Nakano H, et al. High-dose intravenous gammaglobulin for Kawasaki disease. *Lancet*. 1984;2(8411):1055-1058. Available at: https://www.ncbi.nlm.nih.gov/pubmed/6209513.
20. Dove ML, Jaggi P, Kelleman M, et al. Multisystem inflammatory syndrome in children: survey of protocols for early hospital evaluation and management. *J Pediatr*. 2021;229:33-40. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33075369.
21. Chiotos K, Bassiri H, Behrens EM, et al. Multisystem inflammatory syndrome in children during the coronavirus 2019 pandemic: a case series. *J Pediatric Infect Dis Soc*. 2020;9(3):393-398. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32463092.
22. Newburger JW, Sleeper LA, McCrindle BW, et al. Randomized trial of pulsed corticosteroid therapy for primary treatment of Kawasaki disease. *N Engl J Med*. 2007;356(7):663-675. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17301297.
23. Inoue Y, Okada Y, Shinohara M, et al. A multicenter prospective randomized trial of corticosteroids in primary

therapy for Kawasaki disease: clinical course and coronary artery outcome. *J Pediatr*. 2006;149(3):336-341. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16939743.

24. Eloseily EM, Weiser P, Crayne CB, et al. Benefit of anakinra in treating pediatric secondary hemophagocytic lymphohistiocytosis. *Arthritis Rheumatol*. 2020;72(2):326-334. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31513353.
25. Quartier P, Allantaz F, Cimaz R, et al. A multicentre, randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial). *Ann Rheum Dis*. 2011;70(5):747-754. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21173013.
26. Ter Haar NM, van Dijkhuizen EHP, Swart JF, et al. Treatment to target using recombinant interleukin-1 receptor antagonist as first-line monotherapy in new-onset systemic juvenile idiopathic arthritis: results from a five-year follow-up study. *Arthritis Rheumatol*. 2019;71(7):1163-1173. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30848528.
27. Cole LD, Osborne CM, Silveira LJ, et al. IVIG compared to IVIG plus infliximab in multisystem inflammatory syndrome in children. *Pediatrics*. 2021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34548377.
28. Mori M, Hara T, Kikuchi M, et al. Infliximab versus intravenous immunoglobulin for refractory Kawasaki disease: a Phase 3, randomized, open-label, active-controlled, parallel-group, multicenter trial. *Sci Rep*. 2018;8(1):1994. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29386515.
29. Yamaji N, da Silva Lopes K, Shoda T, et al. TNF-alpha blockers for the treatment of Kawasaki disease in children. *Cochrane Database Syst Rev*. 2019;8:CD012448. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31425625.
30. McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. *Circulation*. 2017;135(17):e927-e999. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28356445.
31. Ankola AA, Bradford VR, Newburger JW, et al. Coagulation profiles and viscoelastic testing in multisystem inflammatory syndrome in children. *Pediatr Blood Cancer*. 2021;68(12):e29355. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34532964.
32. Whitworth H, Sartain SE, Kumar R, et al. Rate of thrombosis in children and adolescents hospitalized with COVID-19 or MIS-C. *Blood*. 2021;138(2):190-198. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33895804.
33. Abrams JY, Oster ME, Godfred-Cato SE, et al. Factors linked to severe outcomes in multisystem inflammatory syndrome in children (MIS-C) in the USA: a retrospective surveillance study. *Lancet Child Adolesc Health*. 2021;5(5):323-331. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33711293.
34. Godfred-Cato S, Bryant B, Leung J, et al. COVID-19-associated multisystem inflammatory syndrome in children - United States, March–July 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(32):1074-1080. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32790663.
35. Weiss SL, Peters MJ, Agus MSD, et al. Perspective of the Surviving Sepsis Campaign on the management of pediatric sepsis in the era of coronavirus disease 2019. *Pediatr Crit Care Med*. 2020;21(11):e1031-e1037. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32886460.

Care of Critically Ill Adult Patients With COVID-19

Last Updated: December 16, 2021

Summary Recommendations

Infection Control

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

Hemodynamics

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

Oxygenation and Ventilation

- For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy, the Panel recommends high-flow nasal cannula (HFNC) oxygen over noninvasive ventilation (NIV) **(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** using awake prone positioning as a rescue therapy for refractory hypoxemia to avoid intubation in patients who otherwise meet the indications for intubation and mechanical ventilation **(AIII)**.
- If intubation becomes necessary, the procedure should be performed by an experienced practitioner in a controlled setting due to the enhanced risk of exposing health care practitioners to SARS-CoV-2 during intubation **(AIII)**.
- For mechanically ventilated adults with COVID-19 and acute respiratory distress syndrome (ARDS):
  - The Panel recommends using low tidal volume (VT) ventilation (VT 4–8 mL/kg of predicted body weight) over higher VT ventilation (VT >8 mL/kg) **(AI)**.
  - The Panel recommends targeting plateau pressures of <30 cm H_2O **(AIIa)**.
  - The Panel recommends using a conservative fluid strategy over a liberal fluid strategy **(BIIa)**.
  - The Panel **recommends against** the routine use of **inhaled nitric oxide (AIIa)**.
- For mechanically ventilated adults with COVID-19 and moderate to severe ARDS:
  - The Panel recommends using a higher positive end-expiratory pressure (PEEP) strategy over a lower PEEP strategy **(BIIa)**.
  - For mechanically ventilated adults with COVID-19 and refractory hypoxemia despite optimized ventilation, the Panel recommends prone ventilation for 12 to 16 hours per day over no prone ventilation **(BIIa)**.
  - The Panel recommends using, as needed, intermittent boluses of **neuromuscular blocking agents** (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)**.

Acute Kidney Injury and Renal Replacement Therapy

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

Pharmacologic Interventions

- In patients with COVID-19 and severe or critical illness, there is insufficient evidence for the Panel to recommend either for or against the use of empiric broad-spectrum antimicrobial therapy in the absence of another indication.
- If antimicrobials are initiated, the Panel recommends reassessing the need for them daily to minimize the adverse effects of unnecessary antimicrobial therapy **(AIII)**.

Extracorporeal Membrane Oxygenation

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

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

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

General Considerations

Last Updated: April 21, 2021

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

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

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

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

Comorbid Conditions

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

Bacterial Superinfection of COVID-19-Associated Pneumonia

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

Inflammatory Response Due to COVID-19

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

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

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

Multisystem Inflammatory Syndrome in Adults

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

MIS-A is defined by the following criteria:

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

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

COVID-19-Induced Cardiac Dysfunction, Including Myocarditis

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

Thromboembolic Events and COVID-19

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

Renal and Hepatic Dysfunction Due to COVID-19

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

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

Considerations in Children

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

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

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

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

Sedation Management in Patients With COVID-19

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

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

A. Assess, prevent, and manage pain;

B. Both spontaneous awakening and breathing trials;

C. Choice of analgesia and sedation;

D. Delirium: assess, prevent, and manage;

E. Early mobility and exercise; *and*

F. Family engagement and empowerment.

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

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

Post-Intensive Care Syndrome

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

Post-intensive care syndrome (PICS) is a spectrum of cognitive, psychiatric, and/or physical disability that affects survivors of critical illness and persists after a patient leaves the ICU.[40] Patients with PICS may present with varying levels of impairment; including profound muscle weakness (ICU-acquired weakness); problems with thinking and judgment (cognitive dysfunction); and mental health problems, such as problems sleeping, post-traumatic stress disorder (PTSD), depression, and anxiety. ICU-acquired weakness affects 33% of all patients who receive mechanical ventilation, 50% of patients with sepsis, and ≤50% of patients who remain in the ICU for ≥1 week.[41-43] Cognitive dysfunction affects 30% to 80% of patients discharged from the ICU.[44-46] About 50% of ICU survivors do not return to work within 1 year after discharge.[47] Although no single risk factor has been associated with PICS, there are opportunities to minimize the risk of PICS through medication management (using the A-F Bundle), physical rehabilitation, follow-up clinics, family support, and improved education about the syndrome. PICS also affects family members who participate in the care of their loved ones. In one study, a third of family members who had main decision-making roles experienced mental health problems, such as depression, anxiety, and PTSD.[48]

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

Other Intensive Care Unit-Related Complications

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

Advance Care Planning and Goals of Care

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

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

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

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

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References

1. Alhazzani W, Moller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). *Crit Care Med*. 20200;48(6):e440-e469. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32224769.
2. Centers for Disease Control and Prevention. Evidence used to update the list of underlying medical conditions that increase a person's risk of severe illness from COVID-19. 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/evidence-table.html. Accessed December 8, 2020.
3. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. 2020;180(7):934-943. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32167524.
4. Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington state. *JAMA*. 2020;323(16):1612-1614. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32191259.
5. Bhatraju PK, Ghassemieh BJ, Nichols M, et al. COVID-19 in critically ill patients in the Seattle region—case series. *N Engl J Med*. 2020;382(21):2012-2022. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32227758.
6. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32105632.
7. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ*. 2020;368:m1091. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32217556.
8. Du Y, Tu L, Zhu P, et al. Clinical features of 85 fatal cases of COVID-19 from Wuhan: a retrospective observational study. *Am J Respir Crit Care Med*. 2020;201(11):1372-1379. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32242738.
9. Leisman DE, Ronner L, Pinotti R, et al. Cytokine elevation in severe and critical COVID-19: a rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes. *Lancet Respir Med*. 2020;8(12):1233-1244. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33075298.
10. Sinha P, Matthay MA, Calfee CS. Is a "cytokine storm" relevant to COVID-19? *JAMA Intern Med*. 2020;180(9):1152-1154. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32602883.
11. Morris SB, Schwartz NG, Patel P, et al. Case series of multisystem inflammatory syndrome in adults associated with SARS-CoV-2 infection—United Kingdom and United States, March–August 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(40):1450-1456. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33031361.

12. Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol*. 2020;5(7):802-810. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32211816.

13. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31986264.

14. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32171076.

15. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061-1069. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32031570.

16. Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. *Nat Rev Cardiol*. 2020;17(9):543-558. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32690910.

17. Llitjos JF, Leclerc M, Chochois C, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. *J Thromb Haemost*. 2020;18(7):1743-1746. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32320517.

18. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med*. 2020;46(6):1089-1098. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32367170.

19. Klok FA, Kruip M, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32291094.

20. Menter T, Haslbauer JD, Nienhold R, et al. Postmortem examination of COVID-19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings in lungs and other organs suggesting vascular dysfunction. *Histopathology*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32364264.

21. Tavazzi G, Civardi L, Caneva L, Mongodi S, Mojoli F. Thrombotic events in SARS-CoV-2 patients: an urgent call for ultrasound screening. *Intensive Care Med*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32322918.

22. Sun D, Li H, Lu XX, et al. Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center's observational study. *World J Pediatr*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32193831.

23. Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 Among Children in China. *Pediatrics*. 2020;145(6). Available at: https://www.ncbi.nlm.nih.gov/pubmed/32179660.

24. Centers for Disease Control and Prevention. Coronavirus disease 2019 in children—United States, February 12–April 2, 2020. 2020. Available at: https://www.cdc.gov/mmwr/volumes/69/wr/mm6914e4.htm. Accessed January 5, 2021.

25. Chao JY, Derespina KR, Herold BC, et al. Clinical characteristics and outcomes of hospitalized and critically ill children and adolescents with coronavirus disease 2019 (COVID-19) at a tertiary care medical center in New York City. *J Pediatr*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32407719.

26. Zachariah P, Johnson CL, Halabi KC, et al. Epidemiology, clinical features, and disease severity in patients with coronavirus disease 2019 (COVID-19) in a children's hospital in New York City, New York. *JAMA Pediatr*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32492092.

27. DeBiasi RL, Song X, Delaney M, et al. Severe COVID-19 in children and young adults in the Washington, DC metropolitan region. *J Pediatr*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32405091.

28. Whittaker E, Bamford A, Kenny J, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. *JAMA*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32511692.

29. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32410760.

30. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med*. 2013;41(1):263-306. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23269131.

31. Devlin JW, Skrobik Y, Gelinas C, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med*. 2018;46(9):e825-e873. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30113379.

32. Kress JP, Vinayak AG, Levitt J, et al. Daily sedative interruption in mechanically ventilated patients at risk for coronary artery disease. *Crit Care Med*. 2007;35(2):365-371. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17205005.

33. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet*. 2008;371(9607):126-134. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18191684.

34. Society of Critical Care Medicine. ICU Liberation Bundle (A-F). Available at: https://www.sccm.org/ICULiberation/ABCDEF-Bundles. Accessed January 5, 2021.

35. Barnes-Daly MA, Phillips G, Ely EW. Improving hospital survival and reducing brain dysfunction at seven California community hospitals: implementing PAD guidelines via the ABCDEF bundle in 6,064 patients. *Crit Care Med*. 2017;45(2):171-178. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27861180.

36. Helms J, Kremer S, Merdji H, et al. Neurologic features in severe SARS-CoV-2 infection. *N Engl J Med*. 2020;382(23):2268-2270. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32294339.

37. Pun BT, Badenes R, Heras La Calle G, et al. Prevalence and risk factors for delirium in critically ill patients with COVID-19 (COVID-D): a multicentre cohort study. *Lancet Respir Med*. 2021;9(3):239-250. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33428871.

38. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol*. 2020;77(6):683-690. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32275288.

39. Solomon IH, Normandin E, Bhattacharyya S, et al. Neuropathological features of COVID-19. *N Engl J Med*. 2020;383(10):989-992. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32530583.

40. Society of Critical Care Medicine. Post-intensive care syndrome. 2013. Available at: https://www.sccm.org/MyICUCare/THRIVE/Post-intensive-Care-Syndrome. Accessed September 22, 2020.

41. Fan E, Dowdy DW, Colantuoni E, et al. Physical complications in acute lung injury survivors: a two-year longitudinal prospective study. *Crit Care Med*. 2014;42(4):849-859. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24247473.

42. De Jonghe B, Sharshar T, Lefaucheur JP, et al. Paresis acquired in the intensive care unit: a prospective multicenter study. *JAMA*. 2002;288(22):2859-2867. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12472328.

43. Ali NA, O'Brien JM, Jr., Hoffmann SP, et al. Acquired weakness, handgrip strength, and mortality in critically ill patients. *Am J Respir Crit Care Med*. 2008;178(3):261-268. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18511703.

44. Pandharipande PP, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. *N Engl J Med*. 2013;369(14):1306-1316. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24088092.

45. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA*. 2010;304(16):1787-1794. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20978258.

46. Mikkelsen ME, Christie JD, Lanken PN, et al. The adult respiratory distress syndrome cognitive outcomes study: long-term neuropsychological function in survivors of acute lung injury. *Am J Respir Crit Care Med*.

2012;185(12):1307-1315. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22492988.

47. Kamdar BB, Sepulveda KA, Chong A, et al. Return to work and lost earnings after acute respiratory distress syndrome: a 5-year prospective, longitudinal study of long-term survivors. *Thorax*. 2018;73(2):125-133. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28918401.
48. Azoulay E, Pochard F, Kentish-Barnes N, et al. Risk of post-traumatic stress symptoms in family members of intensive care unit patients. *Am J Respir Crit Care Med*. 2005;171(9):987-994. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15665319.
49. Carfi A, Bernabei R, Landi F, Gemelli Against C-P-ACSG. Persistent symptoms in patients after acute COVID-19. *JAMA*. 2020;324(6):603-605. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32644129.

Infection Control

Last Updated: October 9, 2020

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

Recommendation

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

Rationale

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

Recommendation

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

Rationale

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

Recommendations

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

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

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

Rationale

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

Recommendations

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

Rationale

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

References

1. Yam LY, Chen RC, Zhong NS. SARS: ventilatory and intensive care. *Respirology*. 2003;8 Suppl:S31-35. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15018131.
2. Twu SJ, Chen TJ, Chen CJ, et al. Control measures for severe acute respiratory syndrome (SARS) in Taiwan. *Emerg Infect Dis*. 2003;9(6):718-720. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12781013.
3. Centers for Disease Control and Prevention. The National Personal Protective Technology Laboratory (NPPTL): respirator trusted-source information. 2020. Available at: https://www.cdc.gov/niosh/npptl/topics/respirators/disp_part/respsource.html. Accessed September 23, 2020.
4. Milton DK, Fabian MP, Cowling BJ, Grantham ML, McDevitt JJ. Influenza virus aerosols in human exhaled breath: particle size, culturability, and effect of surgical masks. *PLoS Pathog*. 2013;9(3):e1003205. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23505369.
5. Qian H, Li Y, Sun H, Nielsen PV, Huang X, Zheng X. Particle removal efficiency of the portable HEPA air cleaner in a simulated hospital ward. *Building Simulation*. 2010;3:215-224. Available at: https://link.springer.com/article/10.1007/s12273-010-0005-4.
6. Offeddu V, Yung CF, Low MSF, Tam CC. Effectiveness of masks and respirators against respiratory infections in healthcare workers: a systematic review and meta-analysis. *Clin Infect Dis*. 2017;65(11):1934-1942. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29140516.
7. Bartoszko JJ, Farooqi MAM, Alhazzani W, Loeb M. Medical masks vs N95 respirators for preventing

COVID-19 in healthcare workers: a systematic review and meta-analysis of randomized trials. *Influenza Other Respir Viruses*. 2020;14(4):365-373. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32246890.

8. Tran K, Cimon K, Severn M, Pessoa-Silva CL, Conly J. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review. *PLoS One*. 2012;7(4):e35797. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22563403.
9. Lewis SR, Butler AR, Parker J, Cook TM, Schofield-Robinson OJ, Smith AF. Videolaryngoscopy versus direct laryngoscopy for adult patients requiring tracheal intubation: a Cochrane Systematic Review. *Br J Anaesth*. 2017;119(3):369-383. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28969318.

Hemodynamics

Last Updated: July 8, 2021

Most of the hemodynamic recommendations below are similar to those previously published in the *Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016*. Ultimately, adult patients with COVID-19 who require fluid resuscitation or hemodynamic management of shock should be treated and managed identically to adult patients with septic shock.[1]

Recommendation

- For adults with COVID-19 and shock, the COVID-19 Treatment Guidelines Panel (the Panel) recommends using dynamic parameters, skin temperature, capillary refilling time, and/or lactate levels over static parameters to assess fluid responsiveness **(BIIa)**.

Rationale

In a systematic review and meta-analysis of 13 randomized clinical trials in intensive care unit (ICU) patients without COVID-19 (n = 1,652),[2] dynamic assessment to guide fluid therapy reduced mortality (risk ratio 0.59; 95% CI, 0.42–0.83), ICU length of stay (weighted mean difference -1.16 days; 95% CI, -1.97 to -0.36), and duration of mechanical ventilation (weighted mean difference -2.98 hours; 95% CI, -5.08 to -0.89). Dynamic parameters used in these trials included stroke volume variation (SVV), pulse pressure variation (PPV), and stroke volume change with passive leg raise or fluid challenge. Passive leg raising, followed by PPV and SVV, appears to predict fluid responsiveness with the greatest accuracy.[3] The static parameters included components of early goal-directed therapy (e.g., central venous pressure, mean arterial pressure [MAP]).

Resuscitation of patients with shock who do not have COVID-19 based on serum lactate levels has been summarized in a systematic review and meta-analysis of seven randomized clinical trials (n = 1,301). Compared with central venous oxygen saturation-guided therapy, early lactate clearance-directed therapy was associated with a reduction in mortality (relative ratio 0.68; 95% CI, 0.56–0.82), shorter ICU stay (mean difference -1.64 days; 95% CI, -3.23 to -0.05), and shorter duration of mechanical ventilation (mean difference -10.22 hours; 95% CI, -15.94 to -4.50).[4]

Recommendation

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

Rationale

A pragmatic randomized trial compared the use of balanced and unbalanced crystalloids for intravenous (IV) fluid administration in critically ill adults without COVID-19 (n = 15,802). The rate of the composite outcome of death, new renal-replacement therapy, or persistent renal dysfunction was lower in the balanced crystalloids group than in the unbalanced crystalloids group (OR 0.90; 95% CI, 0.82–0.99; $P = 0.04$).[5] A secondary analysis compared outcomes in a subset of patients with sepsis (n = 1,641). Compared to treatment with unbalanced crystalloids, treatment with balanced crystalloids resulted in fewer deaths (aOR 0.74; 95% CI, 0.59–0.93; $P = 0.01$) and more vasopressor-free and renal replacement-free days.[6] A subsequent meta-analysis of 21 non-COVID-19 randomized controlled trials (n = 20,213) that included the pragmatic trial cited above compared balanced crystalloids to 0.9% saline for resuscitation of critically ill adults and children. The trial reported nonsignificant differences between the treatment groups in hospital mortality (OR 0.91; 95% CI, 0.83–1.01) and acute kidney injury (OR

0.92; 95% CI, 0.84–1.00).[7]

Recommendation

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

Rationale

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

Recommendation

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

Rationale

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

Recommendation

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

Rationale

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

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

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

- The Panel **recommends against** using hydroxyethyl starches for intravascular volume replacement in adult patients with COVID-19 and sepsis or septic shock **(AI)**.
- When norepinephrine is available, the Panel **recommends against** using **dopamine** for adult patients with COVID-19 and shock **(AI)**.
- As a second line vasopressor, the Panel recommends adding either **vasopressin** (up to 0.03 units/min) **(BIIa)** or **epinephrine (BIIb)** to norepinephrine to raise MAP to target or adding vasopressin (up to 0.03 units/min) **(BIIa)** to decrease norepinephrine dosage.
- The Panel **recommends against** using **low-dose dopamine** for renal protection **(AI)**.
- The Panel recommends using **dobutamine** in adult patients with COVID-19 who show evidence of cardiac dysfunction and persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents **(BIII)**.
- The Panel recommends that all adult patients with COVID-19 who require vasopressors have an arterial catheter placed as soon as practical, if resources are available **(BIII)**.
- For adult patients with refractory septic shock who have completed a course of corticosteroids to treat COVID-19, the Panel recommends using low-dose corticosteroid therapy ("shock-reversal") over no corticosteroid therapy **(BIIa)**.
  - A typical corticosteroid regimen in septic shock is hydrocortisone 200 mg IV per day administered either as an infusion or in intermittent doses. The duration of hydrocortisone therapy is usually a clinical decision.
  - Adult patients who are receiving corticosteroids for COVID-19 are receiving sufficient replacement therapy such that they do not require additional hydrocortisone.

References

1. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. *Crit Care Med*. 2017;45(3):486-552. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28098591.
2. Bednarczyk JM, Fridfinnson JA, Kumar A, et al. Incorporating dynamic assessment of fluid responsiveness into goal-directed therapy: a systematic review and meta-analysis. *Crit Care Med*. 2017;45(9):1538-1545. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28817481.
3. Bentzer P, Griesdale DE, Boyd J, MacLean K, Sirounis D, Ayas NT. Will this hemodynamically unstable patient respond to a bolus of intravenous fluids? *JAMA*. 2016;316(12):1298-1309. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27673307.
4. Pan J, Peng M, Liao C, Hu X, Wang A, Li X. Relative efficacy and safety of early lactate clearance-guided therapy resuscitation in patients with sepsis: a meta-analysis. *Medicine (Baltimore)*. 2019;98(8):e14453. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30813144.
5. Semler MW, Self WH, Wanderer JP, et al. Balanced crystalloids versus saline in critically ill adults. *N Engl J Med*. 2018;378(9):829-839. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29485925.
6. Brown RM, Wang L, Coston TD, et al. Balanced crystalloids versus saline in sepsis. A secondary analysis of

the SMART clinical trial. *Am J Respir Crit Care Med*. 2019;200(12):1487-1495. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31454263.

7. Antequera Martin AM, Barea Mendoza JA, Muriel A, et al. Buffered solutions versus 0.9% saline for resuscitation in critically ill adults and children. *Cochrane Database Syst Rev*. 2019;7:CD012247. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31334842.
8. Lewis SR, Pritchard MW, Evans DJ, et al. Colloids versus crystalloids for fluid resuscitation in critically ill people. *Cochrane Database Syst Rev*. 2018;8:CD000567. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30073665.
9. Delaney AP, Dan A, McCaffrey J, Finfer S. The role of albumin as a resuscitation fluid for patients with sepsis: a systematic review and meta-analysis. *Crit Care Med*. 2011;39(2):386-391. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21248514.
10. Regnier B, Rapin M, Gory G, Lemaire F, Teisseire B, Harari A. Haemodynamic effects of dopamine in septic shock. *Intensive Care Med*. 1977;3(2):47-53. Available at: https://www.ncbi.nlm.nih.gov/pubmed/893773.
11. Beck G, Brinkkoetter P, Hanusch C, et al. Clinical review: immunomodulatory effects of dopamine in general inflammation. *Crit Care*. 2004;8(6):485-491. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15566620.
12. Avni T, Lador A, Lev S, Leibovici L, Paul M, Grossman A. Vasopressors for the treatment of septic shock: systematic review and meta-analysis. *PLoS One*. 2015;10(8):e0129305. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26237037.
13. Regnier B, Safran D, Carlet J, Teisseire B. Comparative haemodynamic effects of dopamine and dobutamine in septic shock. *Intensive Care Med*. 1979;5(3):115-120. Available at: https://www.ncbi.nlm.nih.gov/pubmed/500939.
14. De Backer D, Creteur J, Silva E, Vincent JL. Effects of dopamine, norepinephrine, and epinephrine on the splanchnic circulation in septic shock: which is best? *Crit Care Med*. 2003;31(6):1659-1667. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12794401.
15. Lamontagne F, Day AG, Meade MO, et al. Pooled analysis of higher versus lower blood pressure targets for vasopressor therapy septic and vasodilatory shock. *Intensive Care Med*. 2018;44(1):12-21. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29260272.
16. Lamontagne F, Richards-Belle A, Thomas K, et al. Effect of reduced exposure to vasopressors on 90-day mortality in older critically ill patients with vasodilatory hypotension: a randomized clinical trial. *JAMA*. 2020;323(10):938-949. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32049269.

Oxygenation and Ventilation

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

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

Goal of Oxygenation

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

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

The results of a meta-analysis of 25 randomized trials that involved patients without COVID-19 demonstrate the potential harm of maintaining an SpO_2 of >96%. This study found that a liberal oxygen strategy (median SpO_2 of 96%) was associated with an increased risk of in-hospital mortality when compared to a more conservative SpO_2 strategy (relative risk 1.21; 95% CI, 1.03–1.43).[2]

Acute Hypoxemic Respiratory Failure

In adults with COVID-19 and acute hypoxemic respiratory failure, conventional oxygen therapy may be insufficient to meet the oxygen needs of the patient. Options for providing enhanced respiratory support include high-flow nasal canula (HFNC) oxygen, noninvasive 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 positive pressure ventilation 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 HFNC oxygen over NIV **(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; this guidance is based on data from an unblinded clinical trial in patients without COVID-19 who had acute hypoxemic respiratory failure. Study participants were randomized to receive HFNC oxygen, conventional oxygen therapy, or NIV. The patients in the HFNC oxygen arm had more ventilator-free days (mean of 24 days) than those in the conventional oxygen therapy arm (mean of 22 days) or NIV arm (mean of 19 days; $P = 0.02$). In addition, 90-day mortality was lower in the HFNC oxygen arm than in either the conventional oxygen therapy arm (HR 2.01; 95% CI, 1.01–3.99) or the NIV arm (HR 2.50; 95% CI, 1.31–4.78).[3] In the subgroup of more severely hypoxemic patients (those with a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen [PaO_2/FiO_2] ≤200 mm Hg), the intubation rate was lower for the HFNC oxygen arm than for the conventional oxygen therapy or NIV arms (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 was conducted to assess the effectiveness of oxygenation strategies prior to intubation. Compared to NIV, HFNC oxygen reduced the rate of intubation (OR 0.48; 95% CI, 0.31–0.73) and intensive care unit (ICU) mortality (OR 0.36; 95% CI, 0.20–0.63).[4]

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

Awake Prone Positioning in Nonmechanically Ventilated Adults

Recommendations

- For patients with persistent hypoxemia who require HFNC oxygen and for whom endotracheal intubation is not indicated, the Panel recommends a trial of awake prone positioning **(BIIa)**.
- The Panel **recommends against** using awake prone positioning as a rescue therapy for refractory hypoxemia to avoid intubation in patients who otherwise meet the indications for intubation and 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.[7]
- Some patients do not tolerate awake prone positioning. Failure rates as high as 63% have been reported in the literature.[8]
- Awake proning **should not be used** as a substitute for intubation and mechanical ventilation in patients with refractory hypoxemia who otherwise meet the indications for these interventions.
- Awake proning may be infeasible or impractical in patients with:
  - Spinal instability
  - Facial or pelvic fractures
  - An open chest or unstable chest wall
- Awake prone positioning should be used with caution in patients with confusion or delirium, hemodynamic instability, an inability to independently change position, recent abdominal surgery, or recent nausea or vomiting.

Rationale

Awake proning, 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,[9,10] 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 similarly reported that awake prone positioning improves oxygenation,[11-14] and some series have also reported low intubation rates after proning.[11,13]

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

The study enrolled 1,126 patients between April 2, 2020, and January 26, 2021; the intention-to-treat analysis included 1,121 patients. Two hundred twenty-three of 564 patients (40%) who underwent awake prone positioning met the primary composite outcome of intubation or death within 28 days of enrollment; among the 557 patients who received standard care, 257 (46%) met the primary endpoint (relative risk 0.86; 95% CI, 0.75−0.98). Regarding the individual components of the composite endpoint, the incidence of intubation at Day 28 was lower in the awake prone positioning arm than in the standard care arm (HR for intubation 0.75; 95% CI, 0.62−0.91). There was no difference in 28-day mortality between the awake prone positioning arm and the standard care arm (HR for mortality 0.87; 95% CI, 0.68−1.11). During the first 14 days of the study, the median daily duration of awake prone positioning was 5.0 hours (IQR 1.6–8.8 hours). However, the median daily duration varied from 1.6 hours to 8.6 hours across the individual trials. Longer daily durations for awake prone positioning occurred more frequently in patients who experienced treatment success by Day 28. This study evaluated the incidences of certain adverse events, including skin breakdown, vomiting, and central or arterial line dislodgement. These events occurred infrequently during the study, and the incidences for these events were similar between the arms. No cardiac arrests occurred during awake prone positioning.[15]

Though the optimal daily duration of awake prone positioning is unclear, only 25 of 151 patients (17%) who had an average of ≥8 hours of awake prone positioning per day met the primary endpoint of intubation or death in the Awake Prone Positioning Meta-Trial, compared with 198 of 413 patients (48%) who remained in awake prone positioning for <8 hours per day. This is consistent with past clinical trials of prone positioning in mechanically ventilated patients with ARDS, during which clinical benefits were observed with longer durations of prone positioning.[9,10]

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 Acute Respiratory Distress Syndrome

Recommendations

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

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

Rationale

PEEP is beneficial in patients with ARDS because it prevents alveolar collapse, improves oxygenation, and minimizes atelectotrauma, a source of ventilator-induced lung injury. A meta-analysis of individual patient data from the 3 largest trials that compared lower and higher levels of PEEP in patients without COVID-19 found lower rates of ICU mortality and in-hospital mortality with higher levels of PEEP in those with moderate (PaO_2/FiO_2 100–200 mm Hg) and severe ARDS (PaO_2/FiO_2 <100 mm Hg).[16]

Although there is no clear standard as to what constitutes a high level of PEEP, a conventional threshold is >10 cm H_2O.[17] Recent reports have suggested that, in contrast to patients with non-COVID-19 causes of ARDS, some patients with moderate or severe ARDS due to COVID-19 have normal static lung compliance. In these patients, higher PEEP levels may cause harm by compromising hemodynamics and cardiovascular performance.[18,19] Other studies reported that patients with moderate to severe ARDS due to COVID-19 had low lung compliance, similar to the lung compliance seen in patients with conventional ARDS.[20-23] These seemingly contradictory observations suggest that COVID-19 patients with ARDS are a heterogeneous population, and assessment for responsiveness to higher 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.[9] A meta-analysis evaluated the results of the PROSEVA study and 7 other randomized controlled trials that investigated the use of prone positioning in people with ARDS. The subgroup analysis revealed that patients who remained prone for ≥12 hours per day had a lower mortality rate than those who remained in the supine position (risk ratio 0.74; 95% CI, 0.56–0.99). Prone positioning improved oxygenation in all of the trials; patients in the prone positioning arms had higher PaO_2/FiO_2 on Day 4 than those in the supine positioning arms (mean difference of 23.5 mm Hg; 95% CI, 12.4–34.5).[24]

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

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

Recommendations

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

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

Rationale

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

Rescue Therapies for Mechanically Ventilated Adults With Acute Respiratory Distress Syndrome

Recommendations

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

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

Rationale

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 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.[25] Because recruitment maneuvers can cause barotrauma or hypotension, patients should be closely monitored during recruitment maneuvers. If a patient decompensates during recruitment maneuvers, the maneuver should be stopped immediately. The importance of properly performing recruitment maneuvers was illustrated by an analysis of 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). A subgroup analysis found that traditional recruitment maneuvers significantly reduced hospital mortality (risk ratio 0.85; 95% CI, 0.75–0.97), whereas incremental PEEP titration recruitment maneuvers increased mortality (risk ratio 1.06; 95% CI, 0.97–1.17).[26]

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

References

1. Barrot L, Asfar P, Mauny F, et al. Liberal or conservative oxygen therapy for acute respiratory distress syndrome. *N Engl J Med*. 2020;382(11):999-1008. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32160661.
2. Chu DK, Kim LH, Young PJ, et al. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. *Lancet*. 2018;391(10131):1693-1705. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29726345.
3. Frat JP, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med*. 2015;372(23):2185-2196. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25981908.
4. Ni YN, Luo J, Yu H, Liu D, Liang BM, Liang ZA. The effect of high-flow nasal cannula in reducing the mortality and the rate of endotracheal intubation when used before mechanical ventilation compared with conventional oxygen therapy and noninvasive positive pressure ventilation. A systematic review and meta-analysis. *Am J Emerg Med*. 2018;36(2):226-233. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28780231.
5. Tran K, Cimon K, Severn M, Pessoa-Silva CL, Conly J. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review. *PLoS One*. 2012;7(4):e35797. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22563403.
6. Yu IT, Xie ZH, Tsoi KK, et al. Why did outbreaks of severe acute respiratory syndrome occur in some hospital wards but not in others? *Clin Infect Dis*. 2007;44(8):1017-1025. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17366443.
7. Society for Maternal-Fetal Medicine. Management considerations for pregnant patients with COVID-19. 2020. Available at: https://s3.amazonaws.com/cdn.smfm.org/media/2336/SMFM_COVID_Management_of_COVID_pos_preg_patients_4-30-20_final.pdf.

8. Hallifax RJ, Porter BM, Elder PJ, et al. Successful awake proning is associated with improved clinical outcomes in patients with COVID-19: single-centre high-dependency unit experience. *BMJ Open Respir Res*. 2020;7(1). Available at: https://www.ncbi.nlm.nih.gov/pubmed/32928787.
9. Guerin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med*. 2013;368(23):2159-2168. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23688302.
10. Fan E, Del Sorbo L, Goligher EC, et al. An official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice guideline: mechanical ventilation in adult patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2017;195(9):1253-1263. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28459336.
11. Sun Q, Qiu H, Huang M, Yang Y. Lower mortality of COVID-19 by early recognition and intervention: experience from Jiangsu Province. *Ann Intensive Care*. 2020;10(1):33. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32189136.
12. Elharrar X, Trigui Y, Dols AM, et al. Use of prone positioning in nonintubated patients with COVID-19 and hypoxemic acute respiratory failure. *JAMA*. 2020;323(22):2336-2338. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32412581.
13. Sartini C, Tresoldi M, Scarpellini P, et al. Respiratory parameters in patients with COVID-19 after using noninvasive ventilation in the prone position outside the intensive care unit. *JAMA*. 2020;323(22):2338-2340. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32412606.
14. Caputo ND, Strayer RJ, Levitan R. Early self-proning in awake, non-intubated patients in the emergency department: a single ED's experience during the COVID-19 pandemic. *Acad Emerg Med*. 2020;27(5):375-378. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32320506.
15. Ehrmann S, Li J, Ibarra-Estrada M, et al. Awake prone positioning for COVID-19 acute hypoxaemic respiratory failure: a randomised, controlled, multinational, open-label meta-trial. *Lancet Respir Med*. 2021; Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34425070.
16. Briel M, Meade M, Mercat A, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *JAMA*. 2010;303(9):865-873. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20197533.
17. Alhazzani W, Moller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). *Crit Care Med*. 2020;48(6):e440-e469. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32224769.
18. Marini JJ, Gattinoni L. Management of COVID-19 respiratory distress. *JAMA*. 2020;323(22):2329-2330. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32329799.
19. Tsolaki V, Siempos I, Magira E, Kokkoris S, Zakynthinos GE, Zakynthinos S. PEEP levels in COVID-19 pneumonia. *Crit Care*. 2020;24(1):303. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32505186.
20. Bhatraju PK, Ghassemieh BJ, Nichols M, et al. COVID-19 in critically ill patients in the Seattle region—case series. *N Engl J Med*. 2020;382(21):2012-2022. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32227758.
21. Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. *Lancet*. 2020;395(10239):1763-1770. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32442528.
22. Ziehr DR, Alladina J, Petri CR, et al. Respiratory pathophysiology of mechanically ventilated patients with COVID-19: a cohort study. *Am J Respir Crit Care Med*. 2020;201(12):1560-1564. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32348678.
23. Schenck EJ, Hoffman K, Goyal P, et al. Respiratory mechanics and gas exchange in COVID-19-associated respiratory failure. *Ann Am Thorac Soc*. 2020;17(9):1158-1161. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32432896.
24. Munshi L, Del Sorbo L, Adhikari NKJ, et al. Prone position for acute respiratory distress syndrome. A systematic review and meta-analysis. *Ann Am Thorac Soc*. 2017;14(Supplement_4):S280-S288. Available at:

https://www.ncbi.nlm.nih.gov/pubmed/29068269.

25. Goligher EC, Hodgson CL, Adhikari NKJ, et al. Lung recruitment maneuvers for adult patients with acute respiratory distress syndrome. a systematic review and meta-analysis. *Ann Am Thorac Soc*. 2017;14(Supplement_4):S304-S311. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29043837.
26. Alhazzani W, Moller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Intensive Care Med*. 2020;46(5):854-887. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32222812.
27. Gebistorf F, Karam O, Wetterslev J, Afshari A. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) in children and adults. *Cochrane Database Syst Rev*. 2016(6):CD002787. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27347773.

Acute Kidney Injury and Renal Replacement Therapy

Last Updated: December 17, 2020

Recommendations

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

Rationale

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

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

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

References

1. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5,700 patients hospitalized with COVID-19 in the New York City area. *JAMA*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32320003.
2. American Society of Nephrology. Recommendations on the care of hospitalized patients with COVID-19 and kidney failure requiring renal replacement therapy. 2020. Available at: https://www.asn-online.org/g/blast/files/AKI_COVID-19_Recommendations_Document_03.21.2020.pdf. Accessed November 20, 2020.
3. Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19): considerations for providing hemodialysis to patients with suspected or confirmed COVID-19 in acute care settings. 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/dialysis/dialysis-in-acute-care.html. Accessed November 19, 2020.

Pharmacologic Interventions

Last Updated: July 8, 2021

Therapeutic Management of Adults With COVID-19

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

Immune-Based Therapy

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

Adjunctive Therapy

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

Empiric Broad-Spectrum Antimicrobial Therapy

Recommendations

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

Rationale

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

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

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

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

Extracorporeal Membrane Oxygenation

Last Updated: December 17, 2020

Recommendation

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

Rationale

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

The clinical outcomes for patients with ARDS who are treated with ECMO are variable and depend on multiple factors, including the etiology of hypoxemic respiratory failure, the severity of pulmonary and extrapulmonary illness, the presence of comorbidities, and the ECMO experience of the individual center.[5-7] A recent case series of 83 COVID-19 patients in Paris reported a 60-day mortality of 31% for patients on ECMO.[8] This mortality was similar to the mortality observed in a 2018 study of non-COVID-19 patients with ARDS who were treated with ECMO during the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial; that study reported a mortality of 35% at Day 60.[3]

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

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

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

References

1. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet*. 2009;374(9698):1351-1363. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19762075.
2. Pham T, Combes A, Roze H, et al. Extracorporeal membrane oxygenation for pandemic influenza A(H1N1)-induced acute respiratory distress syndrome: a cohort study and propensity-matched analysis. *Am J Respir Crit Care Med*. 2013;187(3):276-285. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23155145.
3. Combes A, Hajage D, Capellier G, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med*. 2018;378(21):1965-1975. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29791822.

4. Munshi L, Walkey A, Goligher E, Pham T, Uleryk EM, Fan E. Venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: a systematic review and meta-analysis. *Lancet Respir Med*. 2019;7(2):163-172. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30642776.
5. Bullen EC, Teijeiro-Paradis R, Fan E. How I select which patients with ARDS should be treated with venovenous extracorporeal membrane oxygenation. *Chest*. 2020;158(3):1036-1045. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32330459.
6. Henry BM, Lippi G. Poor survival with extracorporeal membrane oxygenation in acute respiratory distress syndrome (ARDS) due to coronavirus disease 2019 (COVID-19): Pooled analysis of early reports. *J Crit Care*. 2020;58:27-28. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32279018.
7. Mustafa AK, Alexander PJ, Joshi DJ, et al. Extracorporeal membrane oxygenation for patients with COVID-19 in severe respiratory failure. *JAMA Surg*. 2020;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32780089.
8. Schmidt M, Hajage D, Lebreton G, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome associated with COVID-19: a retrospective cohort study. *Lancet Respir Med*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32798468.
9. Barbaro RP, MacLaren G, Boonstra PS, et al. Extracorporeal membrane oxygenation support in COVID-19: an international cohort study of the Extracorporeal Life Support Organization registry. *Lancet*. 2020;396(10257):1071-1078. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32987008.

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

Last Updated: February 24, 2022

Summary Recommendations

Remdesivir is the only drug that is approved by the Food and Drug Administration (FDA) for the treatment of COVID-19. Ritonavir-boosted nirmatrelvir (Paxlovid), molnupiravir, and certain anti-SARS-CoV-2 monoclonal antibodies (mAbs) have received Emergency Use Authorizations from the FDA for the treatment of COVID-19.
This section focuses on the COVID-19 Treatment Guidelines Panel's (the Panel) recommendations for using small-molecule antiviral drugs to treat COVID-19. These recommendations are based on the available data; for more information, see Table 2f. For recommendations and information regarding the use of anti-SARS-CoV-2 mAbs, see Anti-SARS-CoV-2 Monoclonal Antibodies and Table 3c.
Recommendations for Treating Nonhospitalized Patients
• The Panel recommends the use of the following anti-SARS-CoV-2 therapies for the treatment of COVID-19. These drugs are listed in order of preference:
  • **Ritonavir-boosted nirmatrelvir (Paxlovid) (AIIa)**
  • **Sotrovimab (AIIa)**
  • **Remdesivir (BIIa)**
  • **Molnupiravir (CIIa)**
• See Therapeutic Management of Nonhospitalized Adults With COVID-19 for detailed recommendations.
Recommendations for Treating Hospitalized Patients
• See Therapeutic Management of Hospitalized Adults With COVID-19 for the Panel's recommendations on using remdesivir with or without immunomodulators in certain hospitalized patients.
Antiviral Drugs With Insufficient Evidence to Support a Recommendation
• There is insufficient evidence for the Panel to recommend either for or against the use of ivermectin for the treatment of COVID-19.
Antiviral Drugs That the Panel Recommends Against
• The Panel **recommends against** the use of the following drugs for the treatment of COVID-19, except in a clinical trial:
  • **Interferons** for nonhospitalized patients **(AIIa)**
  • **Interferon alfa** or **lambda** for hospitalized patients **(AIIa)**
  • **Nitazoxanide (BIIa)**
• The Panel **recommends against** the use of the following drugs for the treatment of COVID-19:
  • **Chloroquine** or **hydroxychloroquine** and/or **azithromycin** for hospitalized **(AI)** and nonhospitalized patients **(AIIa)**
  • **Lopinavir/ritonavir** and **other HIV protease inhibitors** for hospitalized **(AI)** and nonhospitalized patients **(AIII)**
  • **Systemic interferon beta** for hospitalized patients **(AI)**

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

Antiviral Therapy

Because SARS-CoV-2 replication leads to many of the clinical manifestations of COVID-19, antiviral therapies are being investigated for the treatment of COVID-19. These drugs prevent viral replication through various mechanisms, including blocking SARS-CoV-2 entry, inhibiting the activity of

SARS-CoV-2 3-chymotrypsin-like protease (3CLpro) and RNA-dependent RNA polymerase (RdRp), and causing lethal viral mutagenesis.[1-3] Because viral replication may be particularly active early in the course of COVID-19, antiviral therapy may have the greatest impact before the illness progresses to the hyperinflammatory state that can characterize the later stages of disease, including critical illness.[4] For this reason, it is necessary to understand the role of antiviral medications in treating mild, moderate, severe, and critical illness in order to optimize treatment for people with COVID-19.

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

References

1. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for molnupiravir. 2021. Available at: https://www.fda.gov/media/155054/download.
2. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for Paxlovid. 2021. Available at: https://www.fda.gov/media/155050/download.
3. Remdesivir (Veklury) [package insert]. Food and Drug Administration. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/214787Orig1s000lbl.pdf.
4. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. *J Heart Lung Transplant*. 2020;39(5):405-407. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32362390.

Remdesivir

Last Updated: February 24, 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 activity against SARS-CoV-2.[1] In a rhesus macaque model of SARS-CoV-2 infection, remdesivir treatment was initiated soon after inoculation; the remdesivir-treated animals had lower virus levels in the lungs and less lung damage than the control animals.[2] Remdesivir is expected to be active against the B.1.1.529 (Omicron) variant of concern.[3,4]

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

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

Recommendations

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

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

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

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

Monitoring and Adverse Effects

Remdesivir can cause gastrointestinal symptoms (e.g., nausea), elevated transaminase levels, an increase

in prothrombin time without a change in the international normalized ratio, and hypersensitivity reactions.

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

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

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

Considerations in Patients With Renal Insufficiency

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

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

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

Drug-Drug Interactions

Currently, no clinical drug-drug interaction studies of remdesivir have been conducted. In vitro, remdesivir is a minor substrate of cytochrome P450 (CYP) 3A4 and a substrate of the drug transporters organic anion transporting polypeptide (OATP) 1B1 and P-glycoprotein. It is also an inhibitor of CYP3A4, OATP1B1, OATP1B3, and multidrug and toxin extrusion protein 1 (MATE1).[5]

Minimal to no reduction in remdesivir exposure is expected when remdesivir is coadministered with dexamethasone, according to information provided by Gilead Sciences (written communication, July 2020).

See Table 2f for more information.

Considerations in Pregnancy

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

Pregnant patients were excluded from the clinical trials that evaluated the safety and efficacy of remdesivir for the treatment of COVID-19, but preliminary reports of remdesivir use in pregnant patients from small studies and case reports are reassuring.[17] Among 86 pregnant and postpartum hospitalized patients with severe COVID-19 who received compassionate use remdesivir, the therapy was well-tolerated, with a low rate of serious adverse effects.[18]

Considerations in Children

Remdesivir is available through an FDA EUA for the treatment of COVID-19 in hospitalized pediatric patients weighing 3.5 kg to <40 kg or aged <12 years and weighing ≥3.5 kg or in nonhospitalized pediatric patients with mild to moderate COVID-19 and at high risk for disease progression. There are insufficient data on the safety and efficacy of using remdesivir to treat COVID-19 in hospitalized or nonhospitalized pediatric patients aged <12 years or weighing <40 kg, because these populations have not been evaluated in clinical trials for remdesivir. The limited data from the compassionate use program and small-case series suggest that remdesivir was well-tolerated in children who met the EUA criteria, but the data on young infants and neonates are extremely limited.[19-23] A clinical trial is currently evaluating the pharmacokinetics of remdesivir in children (ClinicalTrials.gov Identifier NCT04431453).

Clinical Trials

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

References

1. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*. 2020;30(3):269-271. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32020029.
2. Williamson BN, Feldmann F, Schwarz B, et al. Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. *Nature*. 2020;585(7824):273-276. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32516797.
3. Vangeel L, Chiu W, De Jonghe S, et al. Remdesivir, molnupiravir and nirmatrelvir remain active against SARS-CoV-2 Omicron and other variants of concern. *Antiviral Res*. 2022;198:105252. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35085683.
4. Gilead Sciences. Gilead statement on Veklury (remdesivir) and the SARS-CoV-2 Omicron variant. 2021. Available at: https://www.gilead.com/news-and-press/company-statements/gilead-statement-on-veklury-remdesivir-and-the-sars-cov-2-omicron-variant. Accessed February 7, 2022.
5. Remdesivir (Veklury) [package insert]. Food and Drug Administration. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/214787Orig1s000lbl.pdf.
6. Wong CKH, Lau KTK, Au ICH, et al. Optimal timing of remdesivir initiation in hospitalized COVID-19 patients administered with dexamethasone. *Clin Infect Dis*. 2021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34420051.

7. Benfield T, Bodilsen J, Brieghel C, et al. Improved survival among hospitalized patients with coronavirus disease 2019 (COVID-19) treated with remdesivir and dexamethasone. A nationwide population-based cohort study. *Clin Infect Dis*. 2021;73(11):2031-2036. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34111274.
8. Mozaffari E, Chandak A, Zhang Z, et al. Remdesivir treatment in hospitalized patients with COVID-19: a comparative analysis of in-hospital all-cause mortality in a large multi-center observational cohort. *Clin Infect Dis*. 2021;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34596223.
9. Ali K, Azher T, Baqi M, et al. Remdesivir for the treatment of patients in hospital with COVID-19 in Canada: a randomized controlled trial. *CMAJ*. 2022;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35045989.
10. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus remdesivir for hospitalized adults with COVID-19. *N Engl J Med*. 2021;384(9):795-807. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33306283.
11. Rosas IO, Diaz G, Gottlieb RL, et al. Tocilizumab and remdesivir in hospitalized patients with severe COVID-19 pneumonia: a randomized clinical trial. *Intensive Care Med*. 2021;47(11):1258-1270. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34609549.
12. Gottlieb RL, Vaca CE, Paredes R, et al. Early remdesivir to prevent progression to severe COVID-19 in outpatients. *N Engl J Med*. 2022;386(4):305-315. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34937145.
13. European Medicines Agency Committee for Human Medicinal Products. Background review for cyclodextrins used as excipients. 2014. Available at: https://www.ema.europa.eu/en/documents/report/background-review-cyclodextrins-used-excipients-context-revision-guideline-excipients-label-package_en.pdf.
14. Adamsick ML, Gandhi RG, Bidell MR, et al. Remdesivir in patients with acute or chronic kidney disease and COVID-19. *J Am Soc Nephrol*. 2020;31(7):1384-1386. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32513665.
15. Pettit NN, Pisano J, Nguyen CT, et al. Remdesivir use in the setting of severe renal impairment: a theoretical concern or real risk? *Clin Infect Dis*. 2021;73(11):e3990-e3995. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33315065.
16. Ackley TW, McManus D, Topal JE, Cicali B, Shah S. A valid warning or clinical lore: an evaluation of safety outcomes of remdesivir in patients with impaired renal function from a multicenter matched cohort. *Antimicrob Agents Chemother*. 2021;65(2). Available at: https://www.ncbi.nlm.nih.gov/pubmed/33229428.
17. Jorgensen SCJ, Davis MR, Lapinsky SE. A review of remdesivir for COVID-19 in pregnancy and lactation. *J Antimicrob Chemother*. 2021;77(1):24-30. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34427297.
18. Burwick RM, Yawetz S, Stephenson KE, et al. Compassionate use of remdesivir in pregnant women with severe coronavirus disease 2019. *Clin Infect Dis*. 2021;73(11):e3996-e4004. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33031500.
19. Goldman DL, Aldrich ML, Hagmann SHF, et al. Compassionate use of remdesivir in children with severe COVID-19. *Pediatrics*. 2021;147(5). Available at: https://www.ncbi.nlm.nih.gov/pubmed/33883243.
20. Mendez-Echevarria A, Perez-Martinez A, Gonzalez Del Valle L, et al. Compassionate use of remdesivir in children with COVID-19. *Eur J Pediatr*. 2021;180(4):1317-1322. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33200304.
21. Saikia B, Tang J, Robinson S, et al. Neonates with SARS-CoV-2 infection and pulmonary disease safely treated with remdesivir. *Pediatr Infect Dis J*. 2021;40(5):e194-e196. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33847299.
22. Hammad M, Shalaby L, Sidhom I, et al. Management and outcome of coronavirus disease 2019 (COVID-19) in pediatric cancer patients: a single centre experience from a developing country. *Clin Lymphoma Myeloma Leuk*. 2021;21(11):e853-e864. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34420893.
23. Weclawek-Tompol J, Zakrzewska Z, Gryniewicz-Kwiatkowska O, et al. COVID-19 in pediatric cancer patients is associated with treatment interruptions but not with short-term mortality: a Polish national study. *J Hematol Oncol*. 2021;14(1):163. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34635137.

Table 2a. Remdesivir: Selected Clinical Data

Last Updated: February 24, 2022

The clinical trials described in this table do not represent all the trials that the Panel reviewed while developing the recommendations for RDV. The studies summarized below are the randomized controlled trials that have had the greatest impact on the Panel's recommendations. Studies of hospitalized patients are listed first, followed by studies of nonhospitalized patients.

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

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

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

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

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

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

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

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

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

References

1. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of COVID-19—final report. *N Engl J Med*. 2020;383(19):1813-1826. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32445440.
2. Ader F, Bouscambert-Duchamp M, Hites M, et al. Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a Phase 3, randomised, controlled, open-label trial. *Lancet Infect Dis*. 2022;22(2):209-221. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34534511.
3. WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed antiviral drugs for COVID-19—interim WHO Solidarity Trial results. *N Engl J Med*. 2021;384(6):497-511. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33264556.
4. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. *JAMA*. 2020;324(11):1048-1057. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32821939.
5. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 days in patients with severe COVID-19. *N Engl J Med*. 2020;383(19):1827-1837. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32459919.
6. Gottlieb RL, Vaca CE, Paredes R, et al. Early remdesivir to prevent progression to severe COVID-19 in outpatients. *N Engl J Med*. 2022;386(4):305-315. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34937145.

Ritonavir-Boosted Nirmatrelvir (Paxlovid)

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Nirmatrelvir is an orally bioavailable protease inhibitor that is active against M^{PRO}, a viral protease that plays an essential role in viral replication by cleaving the 2 viral polyproteins.[1] It has demonstrated antiviral activity against all coronaviruses that are known to infect humans.[2] Nirmatrelvir is packaged with ritonavir (as Paxlovid), a strong cytochrome P450 (CYP) 3A4 inhibitor and pharmacokinetic boosting agent that has been used to boost HIV protease inhibitors. Coadministration of ritonavir is required to increase nirmatrelvir concentrations to the target therapeutic range.

On December 22, 2021, the Food and Drug Administration issued an Emergency Use Authorization (EUA) for ritonavir-boosted nirmatrelvir for the treatment of patients with mild to moderate COVID-19 aged ≥12 years and weighing ≥40 kg who are within 5 days of symptom onset and at high risk of progressing to severe disease.[3,4]

Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using **nirmatrelvir 300 mg with ritonavir 100 mg (Paxlovid)** orally twice daily for 5 days in nonhospitalized patients with mild to moderate COVID-19 aged ≥12 years and weighing ≥40 kg who are at high risk of disease progression;[3] treatment should be initiated as soon as possible and within 5 days of symptom onset **(AIIa)**.
- Ritonavir-boosted nirmatrelvir has significant and complex drug-drug interactions, primarily due to the ritonavir component of the combination.
- Before prescribing ritonavir-boosted nirmatrelvir, clinicians **should carefully review the patient's concomitant medications**, including over-the-counter medications, herbal supplements, and recreational drugs, to evaluate potential drug-drug interactions.
- The Liverpool COVID-19 Drug Interactions website, Table A below, and the EUA fact sheet for ritonavir-boosted nirmatrelvir can be used to identify and manage drug-drug interactions.

For the Panel's recommendations on the order of preference for outpatient antiviral therapies and the prioritization of outpatient therapies when there are logistical or supply constraints, see Therapeutic Management of Nonhospitalized Adults With COVID-19.

Rationale

The EPIC-HR trial demonstrated that starting ritonavir-boosted nirmatrelvir treatment in nonhospitalized adults with mild to moderate COVID-19 within 5 days of symptom onset reduced the risk of hospitalization or death through Day 28 by 89% compared to placebo.[4] This efficacy is comparable to the efficacies reported for sotrovimab (i.e., 85% relative reduction)[5] and remdesivir (i.e., 87% relative reduction)[6] and greater than the efficacy reported for molnupiravir (i.e., 30% relative reduction).[7]

Ritonavir-boosted nirmatrelvir is expected to be active against the B.1.1.529 (Omicron) variant of concern (VOC), although there is currently a lack of data on the clinical efficacy of ritonavir-boosted nirmatrelvir against this VOC.[8-10] Because of the potential for significant drug-drug interactions with concomitant medications, this regimen may not be a safe choice for all patients (see below for more information).

Clinical Trial Data

The EPIC-HR study was a multinational randomized trial that compared the use of ritonavir-boosted nirmatrelvir given orally 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 participants were randomized within 5 days of symptom onset, were unvaccinated against COVID-19, and had at least 1 risk factor for progression to severe disease.[11] 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 participants enrolled in the trial. The mean age was 46 years, 51% of the participants were men, and 72% were White. Forty-seven percent of the participants tested negative for SARS-CoV-2 antibodies, and 66% started study treatment within 3 days of symptom onset.

Participants 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 and all-cause deaths occurred by Day 28 in 5 of 697 participants (0.72%) in the ritonavir-boosted nirmatrelvir arm and in 44 of 682 participants (6.5%) in the placebo arm. Among the 2,085 participants 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 participants (0.77%) in the ritonavir-boosted nirmatrelvir arm and in 66 of 1,046 participants (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.

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

Additional Considerations

- Nirmatrelvir must be administered with ritonavir to achieve sufficient therapeutic plasma concentrations.
- Patients should complete the 5-day treatment course of ritonavir-boosted nirmatrelvir. It is unknown whether a shorter course is less effective or associated with the emergence of nirmatrelvir-resistant mutations.
- If a patient requires hospitalization after starting treatment, the full treatment course of ritonavir-boosted nirmatrelvir can be completed at the clinician's discretion.
- Ritonavir-boosted nirmatrelvir may be used in patients who are hospitalized for a diagnosis other than COVID-19, provided they have mild to moderate COVID-19, are at high risk of progressing to severe disease, and are within 5 days of symptom onset.
- There are no data on using 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 COVID-19.
- Severely immunocompromised patients can experience prolonged periods of SARS-CoV-2 replication, which may lead to rapid viral evolution. There are theoretical concerns that using a single antiviral agent in these patients may produce antiviral-resistant viruses. Additional studies are needed to assess this risk. The role of combination antiviral therapy in treating severely immunocompromised patients is not yet known.

Monitoring and Adverse Effects

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

The dose should be reduced to nirmatrelvir 150 mg with ritonavir 100 mg twice daily in patients with moderate renal impairment (i.e., those with an estimated glomerular filtration rate [eGFR] of ≥30 to <60 mL/min). Ritonavir-boosted nirmatrelvir **is not recommended** in patients with an eGFR of <30 mL/min until more data are available. The appropriate dose for patients with severe renal impairment has not been determined.

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

Considerations in Pregnancy

The EPIC-HR trial excluded pregnant and lactating individuals. Ritonavir has been used extensively during pregnancy in people with HIV, which suggests that it has an acceptable safety profile during pregnancy. Based on the mechanisms of action for both nirmatrelvir and ritonavir and the available animal data, the Panel would not withhold ritonavir-boosted nirmatrelvir from a pregnant patient if the potential benefits outweighed the potential risks.

Considerations in Children

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

Drug-Drug Interactions

Ritonavir-boosted nirmatrelvir has significant and complex drug-drug interactions, primarily due to the ritonavir component of the combination. Boosting with ritonavir, a strong CYP3A inhibitor, is required to increase the exposure of nirmatrelvir to a concentration that is effective against SARS-CoV-2. However, 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 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.[12] After ritonavir is discontinued, 80% to 90% of CYP3A4 inhibition resolves within 3 days.[13] The time to resolution of inhibition varies based on factors such as the patient's age; therefore, resolution may take longer in some individuals, such as in the elderly. When ritonavir is used for 5 days, its induction properties are less likely to be clinically relevant than when the drug is used chronically (e.g., in people who take HIV protease inhibitors). Both nirmatrelvir and ritonavir are substrates of CYP3A; thus, administering this treatment with or immediately after discontinuing medications that are strong inducers of CYP3A4 (e.g., rifampin) can lead to significant reductions in nirmatrelvir and ritonavir concentrations, which may decrease nirmatrelvir's effectiveness against SARS-CoV-2.

Guidance for Prescribers and Pharmacists

Identify Drug-Drug Interactions

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

recreational drugs.

- Clinicians should refer to resources such as the Liverpool COVID-19 Drug Interactions website, Table A below, and the EUA fact sheet for ritonavir-boosted nirmatrelvir for guidance regarding potential drug-drug interactions.
- Clinicians should consider consulting an expert (e.g., a pharmacist, HIV specialist, and/or the patient's specialist provider[s], if applicable), especially for patients who are receiving highly specialized therapies, such as antineoplastics, neuropsychiatric drugs, and certain immunosuppressants.
- Drug classes of particular concern are those that include drugs that are prone to concentration-dependent toxicities, including certain antiarrhythmics, oral anticoagulants, immunosuppressants, anticonvulsants, antineoplastics, and neuropsychiatric drugs.

Management Strategies for Drug-Drug Interactions

- Before administering ritonavir-boosted nirmatrelvir to a patient, clinicians should assess the potential risks and benefits of using this combination in that patient. In particular, clinicians should assess the availability of other equally effective COVID-19 treatment options that have lower risks of drug interactions.
- Clinicians should consider the magnitude and significance of the potential interaction when choosing management strategies for patients who are receiving ritonavir-boosted nirmatrelvir. Potential strategies include:
  - Adjusting the dose of the concomitant medication,
  - Using an alternative to the concomitant medication,
  - Increasing monitoring for potential adverse reactions to the concomitant medication, *or*
  - Temporarily withholding the concomitant medication.
- Clinicians should use the chosen strategies for the 5-day duration of ritonavir-boosted nirmatrelvir treatment and for at least 3 days after treatment completion. These strategies may need to be continued for a longer duration if ritonavir-boosted nirmatrelvir is initiated in an elderly patient or if the interacting concomitant medication has a long half-life or narrow therapeutic index.
- In settings where using these management strategies is not feasible or where the effectiveness of ritonavir-boosted nirmatrelvir may be compromised, consider using alternative COVID-19 therapies (see Therapeutic Management of Nonhospitalized Adults With COVID-19).
- The dose of ritonavir-boosted nirmatrelvir should not be adjusted to avoid or mitigate a drug-drug interaction with a concomitant medication.
- Patients on ritonavir- or cobicistat-boosted regimens that are used to treat HIV or hepatitis C virus should continue their treatment as indicated while receiving ritonavir-boosted nirmatrelvir. No dose adjustments are required.
- People who take certain recreational drugs, such as recreational fentanyl, will require careful monitoring for adverse effects if they are prescribed ritonavir-boosted nirmatrelvir.
- The EUA for ritonavir-boosted nirmatrelvir suggests that individuals who use products containing ethinyl estradiol for contraception should use a backup, nonhormonal contraceptive method because ritonavir-boosted nirmatrelvir has the potential to decrease ethinyl estradiol levels. However, the enzyme-inducing effects of ritonavir-boosted nirmatrelvir that would lead to lower hormone exposure are not expected to be clinically significant during 5 days of therapy and, therefore, would not be expected to decrease contraceptive effectiveness. In addition, ethinyl

estradiol is always combined with a progestin for contraception. Progestin concentrations are expected to remain similar or increase when ritonavir-boosted nirmatrelvir is used concomitantly with combined hormonal contraception, which maintains the effectiveness of the oral contraceptive.

Patient Counseling on Drug-Drug Interactions

- Patients should be informed of ritonavir-boosted nirmatrelvir's drug-drug interaction potential with concomitant medications, including over-the-counter medicines, herbal supplements, and recreational drugs.
- If a potential drug-drug interaction is identified, the patient should be informed about the interaction and alerted to the signs and symptoms of potential adverse effects.

Table A. Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Outpatient Medications

This table is not a comprehensive list of all the drugs that may interact with ritonavir-boosted nirmatrelvir. This table focuses on concomitant medications that may be prescribed in the outpatient setting. Pharmacists or providers who have experience with prescribing ritonavir-boosted drugs (e.g., HIV specialists) should be consulted when monitoring and managing drug-drug interactions in patients with mild to moderate COVID-19 who are receiving ritonavir-boosted nirmatrelvir and who may be hospitalized for reasons that are not related to COVID-19.

Deviation from these recommendations may be appropriate in certain clinical scenarios. When significant drug-drug interactions are present, providers should exercise clinical judgment when assessing the risks and benefits of using ritonavir-boosted nirmatrelvir and determining the appropriate management strategies for these interactions.

The table below divides medications into 3 categories:

- Concomitant medications that require patients to receive an alternative COVID-19 therapy. For these drugs, drug-drug interaction management strategies are not possible or feasible, or the potential risks of such strategies outweigh the potential benefits. This category includes:
  - Drugs that may cause significant toxicities due to CYP3A4 inhibition and that cannot be stopped or have their doses adjusted; *or*
  - Drugs that are strong CYP3A inducers and may significantly reduce the concentration of ritonavir and nirmatrelvir, potentially leading to a loss of virologic response. Ritonavir-boosted nirmatrelvir cannot be initiated immediately after discontinuing CYP3A inducers due to the delayed offset of induction.
- Concomitant medications that should be temporarily withheld, if clinically appropriate. If withholding is not clinically appropriate, temporarily switching to an alternative concomitant medication or using an alternative COVID-19 therapy should be considered.
- Concomitant medications that should receive dose adjustments. Patients should be monitored closely for adverse effects. If the dose of the concomitant medication cannot be adjusted, consider withholding the medication (if clinically appropriate) or using an alternative concomitant medication or an alternative COVID-19 therapy.

Prescribe an Alternative COVID-19 Therapy For cases where drug-drug interaction management strategies are not possible or feasible, or the potential risks of such strategies outweigh the potential benefits.		
Amiodarone	Flecainide	Propafenone
Apalutamide	Glecaprevir/pibrentasvir	Quinidine
Bosentan	Ivabradine	Rifampin
Carbamazepine	Lumacaftor/ivacaftor	Rifapentine
Clopidogrel[a]	Lumateperone	Sildenafil for PH
Clozapine	Lurasidone	St. John's wort
Disopyramide	Meperidine (pethidine)	Tadalafil for PH
Dofetilide	Midazolam (oral)	Tolvaptan
Dronedarone	Phenobarbital	Vardenafil for PH
Enzalutamide	Phenytoin	Voclosporin
Eplerenone	Pimozide	
Ergot derivatives	Primidone	
Temporarily Withhold Concomitant Medication, If Clinically Appropriate For guidance on restarting the concomitant medication, consult the Liverpool COVID-19 Drug Interactions website.[b] If withholding is not clinically appropriate, use an alternative concomitant medication or COVID-19 therapy.		
Alfuzosin	Estazolam[d]	Rosuvastatin
Aliskiren	Everolimus[f]	Salmeterol
Atorvastatin	Finerenone	Silodosin
Avanafil	Flibanserin	Simvastatin
Chemotherapy[c]	Flurazepam[d]	Sirolimus[f]
Clonazepam[d]	Lomitapide	Suvorexant
Clorazepate[d]	Lovastatin	Tacrolimus[f]
Colchicine[e]	Naloxegol	Ticagrelor
Diazepam[d]	Ranolazine	Triazolam[d]
Eletriptan	Rimegepant	Ubrogepant
Erythromycin	Rivaroxaban[g]	Vorapaxar
Adjust Concomitant Medication Dose and Monitor for Adverse Effects Consult the Liverpool COVID-19 Drug Interactions website[b] for guidance. 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.		
Alprazolam[d]	Darifenacin	Pimavanserin
Amlodipine	Digoxin	Quetiapine
Apixaban	Elexacaftor/tezacaftor/ivacaftor	Rifabutin
Aripiprazole	Eluxadoline	Riociguat
Brexpiprazole	Fentanyl	Saxagliptin
Buspirone	Iloperidone	Sildenafil for ED
Cariprazine	Itraconazole	Ruxolitinib
Chlordiazepoxide[d]	Ivacaftor	Tadalafil for ED
Cilostazol	Ketoconazole	Tamsulosin
Clarithromycin	Maraviroc	Tezacaftor/ivacaftor
Clobazam[d]	Mexiletine	Trazodone
Cyclosporine[f]	Oxycodone	Vardenafil for ED

[a] Reduced effectiveness of clopidogrel is likely. Do not coadminister clopidogrel in patients who are at a very high risk of thrombosis (e.g., those who are within 6 weeks of coronary stenting); consider prescribing an alternative antiplatelet (i.e., prasugrel) or an alternative COVID-19 therapy. For other indications, it may be acceptable to continue clopidogrel if the benefit of ritonavir-boosted nirmatrelvir treatment outweighs the risk of reduced clopidogrel effectiveness.

[b] Additional resources include the EUA fact sheet for ritonavir-boosted nirmatrelvir and the FDA prescribing information for the concomitant medication. These may be consulted for medications that are not found on the Liverpool COVID-19 Drug Interactions website.

[c] Ritonavir-boosted nirmatrelvir may increase concentrations of certain anticancer agents, leading to an increased potential for drug toxicities. These anticancer agents include kinase inhibitors (e.g., abemaciclib, ceritinib, dasatinib, ibrutinib, neratinib, nilotinib), the IDH1 inhibitor ivosidenib, the BCL-2 inhibitor venetoclax, and vinca alkaloids (e.g., vinblastine, vincristine). Please refer to the prescribing information for the anticancer agent and consult the patient's specialist provider. Avoid concomitant administration of ritonavir-boosted nirmatrelvir with ibrutinib, neratinib, ivosidenib, or venetoclax.

[d] Abrupt discontinuation or rapid dose reduction of benzodiazepines may precipitate acute withdrawal reactions.[14] The risk is greatest for patients who have been using higher doses of benzodiazepines over an extended period of time.

[e] Colchicine is contraindicated in patients with severe hepatic or renal impairment due to the potential for serious or life-threatening reactions.

[f] Before prescribing ritonavir-boosted nirmatrelvir to a patient who is receiving this immunosuppressant, consult the patient's specialist provider(s). This immunosuppressant has significant drug-drug interaction potential with ritonavir, and close monitoring may not be feasible. See this statement from the American Society of Transplantation for more information.

[g] If the patient has a high risk of arterial or venous thrombosis (e.g., those who are within 3 months of a stroke, those with a CHA2DS2-VASc score of 7–9, those who are within 1 month of a pulmonary embolism), the patient's primary or specialty provider should be consulted; consider using an alternative anticoagulant or COVID-19 therapy.

Key: BCL-2 = B cell lymphoma 2; CYP = cytochrome P450; ED = erectile dysfunction; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; IDH1 = isocitrate dehydrogenase-1; PH = pulmonary hypertension

References

1. Pillaiyar T, Manickam M, Namasivayam V, Hayashi Y, Jung SH. An overview of severe acute respiratory syndrome-coronavirus (SARS-CoV) 3CL protease inhibitors: peptidomimetics and small molecule chemotherapy. *J Med Chem*. 2016;59(14):6595-6628. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26878082.
2. Owen DR, Allerton CMN, Anderson AS, et al. An oral SARS-CoV-2 M(pro) inhibitor clinical candidate for the treatment of COVID-19. *Science*. 2021;374(6575):1586-1593. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34726479.
3. Centers for Disease Control and Prevention. COVID-19: people with certain medical conditions. 2021. Available at: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Accessed December 27, 2021.
4. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for Paxlovid. 2021. Available at: https://www.fda.gov/media/155050/download.
5. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Early treatment for COVID-19 with SARS-CoV-2 neutralizing antibody sotrovimab. *N Engl J Med*. 2021;385(21):1941-1950. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34706189.
6. Gottlieb RL, Vaca CE, Paredes R, et al. Early remdesivir to prevent progression to severe COVID-19 in outpatients. *N Engl J Med*. 2022;386(4):305-315. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34937145.
7. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for oral treatment of COVID-19 in nonhospitalized patients. *N Engl J Med*. 2022;386(6):509-520. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34914868.
8. Vangeel L, Chiu W, De Jonghe S, et al. Remdesivir, molnupiravir and nirmatrelvir remain active against SARS-CoV-2 Omicron and other variants of concern. *Antiviral Res*. 2022;198:105252. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35085683.
9. Greasley SE, Noell S, Plotnikova O, et al. Structural basis for nirmatrelvir in vitro efficacy against the Omicron variant of SARS-CoV-2. *bioRxiv*. 2022;Preprint. Available at: https://www.biorxiv.org/content/10.1101/2022.01.17.476556v1.
10. Rai DK, Yurgelonis I, McMonagle P, et al. Nirmatrelvir, an orally active MPRO inhibitor, is a potent inhibitor

of SARS-CoV-2 variants of concern. *bioRxiv*. 2022;Preprint. Available at: https://www.biorxiv.org/content/10.1101/2022.01.17.476644v1.

11. Hammond J, Leister-Tebbe H, Gardner A, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with COVID-19. *N Engl J Med*. 2022; Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35172054.
12. Katzenmaier S, Markert C, Riedel KD, et al. Determining the time course of CYP3A inhibition by potent reversible and irreversible CYP3A inhibitors using a limited sampling strategy. *Clin Pharmacol Ther*. 2011;90(5):666-673. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21937987.
13. Stader F, Khoo S, Stoeckle M, et al. Stopping lopinavir/ritonavir in COVID-19 patients: duration of the drug interacting effect. *J Antimicrob Chemother*. 2020;75(10):3084-3086. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32556272.
14. Food and Drug Administration. FDA requiring Boxed Warning updated to improve safe use of benzodiazepine drug class. 2020. Available at: https://www.fda.gov/media/142368/download.

Molnupiravir

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

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

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

Recommendations

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

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

Rationale

In the MOVe-OUT trial, molnupiravir reduced the rate of hospitalization or death by 30% compared to placebo.[4] Even though the different treatment options have not been directly compared in clinical trials,

the Panel recommends using molnupiravir only when ritonavir-boosted nirmatrelvir, sotrovimab, and remdesivir are not available or cannot be given, because molnupiravir has lower efficacy than the other options. For more information, see Therapeutic Management of Nonhospitalized Adults With COVID-19.

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

Additional Considerations

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

Considerations in Sexually Active Individuals

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

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

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

Considerations in Pregnancy

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

There is currently a lack of data on the use of molnupiravir in lactating people, and molnupiravir may

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

Considerations in Children

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

Monitoring, Adverse Effects, and Drug Interactions

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

Clinical Trial Data

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

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

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

References

1. Zhou S, Hill CS, Sarkar S, et al. Beta-d-N4-hydroxycytidine inhibits SARS-CoV-2 through lethal mutagenesis but is also mutagenic to mammalian cells. *J Infect Dis*. 2021;224(3):415-419. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33961695.
2. Kabinger F, Stiller C, Schmitzova J, et al. Mechanism of molnupiravir-induced SARS-CoV-2 mutagenesis. *Nat Struct Mol Biol*. 2021;28(9):740-746. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34381216.
3. Centers for Disease Control and Prevention. COVID-19: people with certain medical conditions. 2021. Available at: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Accessed December 27, 2021.
4. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for molnupiravir. 2021. Available at: https://www.fda.gov/media/155054/download.
5. Fischer WA, 2nd, Eron JJ, Jr., Holman W, et al. A Phase 2a clinical trial of molnupiravir in patients with

COVID-19 shows accelerated SARS-CoV-2 RNA clearance and elimination of infectious virus. *Sci Transl Med*. 2021:eabl7430. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34941423.

6. Vangeel L, De Jonghe S, Piet Maes P, et al. Remdesivir, molnupiravir and nirmatrelvir remain active against SARS-CoV-2 Omicron and other variants of concern. *bioRxiv*. 2022;Preprint. Available at: https://www.biorxiv.org/content/10.1101/2021.12.27.474275v2.
7. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for oral treatment of COVID-19 in nonhospitalized patients. *N Engl J Med*. 2021;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34914868.

Chloroquine or Hydroxychloroquine and/or Azithromycin

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Chloroquine is an antimalarial drug that was developed in 1934. Hydroxychloroquine, an analogue of chloroquine, was developed in 1946. Hydroxychloroquine is used to treat autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis, in addition to malaria.

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

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

Recommendation

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

Rationale

Hospitalized Patients

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

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

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

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

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

Nonhospitalized Patients

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

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

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

Adverse Effects

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

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

Drug-Drug Interactions

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

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

Drug Availability

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

References

1. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*. 2020;30(3):269-271. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32020029.
2. Vincent MJ, Bergeron E, Benjannet S, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. *Virol J*. 2005;2:69. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16115318.
3. Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov*. 2020;6:16. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32194981.
4. Fantini J, Chahinian H, Yahi N. Synergistic antiviral effect of hydroxychloroquine and azithromycin in combination against SARS-CoV-2: what molecular dynamics studies of virus-host interactions reveal. *Int J Antimicrob Agents*. 2020. Available at: https://pubmed.ncbi.nlm.nih.gov/32405156/.
5. Andreani J, Bideau ML, Duflot I, et al. In vitro testing of combined hydroxychloroquine and azithromycin on SARS-CoV-2 shows synergistic effect. *Microb Pathog*. 2020. Available at: https://pubmed.ncbi.nlm.nih.gov/32344177/.
6. Maisonnasse P, Guedj J, Contreras V, et al. Hydroxychloroquine use against SARS-CoV-2 infection in non-human primates. *Nature*. 2020;585(7826):584-587. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32698191.
7. Recovery Collaborative Group, Horby P, Mafham M, et al. Effect of hydroxychloroquine in hospitalized patients with COVID-19. *N Engl J Med*. 2020;383(21):2030-2040. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33031652.
8. WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed antiviral drugs for COVID-19—interim WHO Solidarity Trial results. *N Engl J Med*. 2021;384(6):497-511. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33264556.
9. Self WH, Semler MW, Leither LM, et al. Effect of hydroxychloroquine on clinical status at 14 days in hospitalized patients with COVID-19: a randomized clinical trial. *JAMA*. 2020;324(21):2165-2176. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33165621.
10. Furtado RHM, Berwanger O, Fonseca HA, et al. Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial. *Lancet*. 2020;396(10256):959-967. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32896292.
11. Cavalcanti AB, Zampieri FG, Rosa RG, et al. Hydroxychloroquine with or without azithromycin in mild-to-moderate COVID-19. *N Engl J Med*. 2020;383(21):2041-2052. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32706953.
12. Recovery Collaborative Group. Azithromycin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. 2021;397(10274):605-612. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33545096.
13. Rosenberg ES, Dufort EM, Udo T, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York state. *JAMA*. 2020. Available at:

https://www.ncbi.nlm.nih.gov/pubmed/32392282.

14. Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with COVID-19. *N Engl J Med*. 2020;382(25):2411-2418. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32379955.
15. Arshad S, Kilgore P, Chaudhry ZS, et al. Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. *Int J Infect Dis*. 2020;97:396-403. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32623082.
16. Skipper CP, Pastick KA, Engen NW, et al. Hydroxychloroquine in nonhospitalized adults with early COVID-19: a randomized trial. *Ann Intern Med*. 2020;173(8):623-631. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32673060.
17. Mitja O, Corbacho-Monne M, Ubals M, et al. Hydroxychloroquine for early treatment of adults with mild COVID-19: a randomized-controlled trial. *Clin Infect Dis*. 2020;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32674126.
18. Omrani AS, Pathan SA, Thomas SA, et al. Randomized double-blinded placebo-controlled trial of hydroxychloroquine with or without azithromycin for virologic cure of non-severe COVID-19. *EClinicalMedicine*. 2020. Available at: https://pubmed.ncbi.nlm.nih.gov/33251500/.
19. PRINCIPLE Trial Collaborative Group. Azithromycin for community treatment of suspected COVID-19 in people at increased risk of an adverse clinical course in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. *Lancet*. 2021;397(10279):1063-1074. Available at: https://pubmed.ncbi.nlm.nih.gov/33676597/.
20. Hinks TS, Lucy C, Knight R, et al. A randomised clinical trial of azithromycin versus standard care in ambulatory COVID-19—the ATOMIC2 trial. *medRxiv*. 2021;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.04.21.21255807v1.
21. Nguyen LS, Dolladille C, Drici MD, et al. Cardiovascular toxicities associated with hydroxychloroquine and azithromycin: an analysis of the World Health Organization pharmacovigilance database. *Circulation*. 2020;142(3):303-305. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32442023.
22. Azithromycin (Zithromax) [package insert]. Food and Drug Administration. 2013. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/050710s039,050711s036,050784s023lbl.pdf.
23. Mercuro NJ, Yen CF, Shim DJ, et al. Risk of QT interval prolongation associated with use of hydroxychloroquine with or without concomitant azithromycin among hospitalized patients testing positive for coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2020;5(9):1036-1041. Available at: https://pubmed.ncbi.nlm.nih.gov/32936252/.
24. Chorin E, Wadhwani L, Magnani S, et al. QT interval prolongation and torsade de pointes in patients with COVID-19 treated with hydroxychloroquine/azithromycin. *Heart Rhythm*. 2020;17(9):1425-1433. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32407884.
25. Food and Drug Administration. Remdesivir by Gilead Sciences: FDA warns of newly discovered potential drug interaction that may reduce effectiveness of treatment. 2020. Available at: https://www.fda.gov/safety/medical-product-safety-information/remdesivir-gilead-sciences-fda-warns-newly-discovered-potential-drug-interaction-may-reduce.

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

Last Updated: July 8, 2021

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

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

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

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

Study Design	Methods	Results	Limitations and Interpretation
PETAL Trial: Hydroxychloroquine in Hospitalized Patients With COVID-19[21], continued			
		Outcomes: • Median COVID Outcomes Scale score was 6 in HCQ arm (IQR 4–7) and 6 in placebo arm (IQR 4–7; aOR 1.02; 95% CI, 0.73–1.42). • No difference between the arms in the secondary outcome of all-cause, all-location death at Day 14 and Day 28 • No difference between the arms in the number of any of the following systematically collected safety events: cardiac arrest treated with CPR, symptomatic hypoglycemia, ventricular arrhythmia, or seizure • Among patients who had QTc assessed, 5.9% in HCQ arm and 3.3% in placebo arm had a recorded QTc interval >500 ms during the first 5 days of dosing.	
RECOVERY Trial[22]			
Open-label, randomized controlled platform trial with multiple arms; in 1 arm, hospitalized patients received HCQ (n = 11,197)	**Key Inclusion Criteria:** • Clinically suspected or laboratory-confirmed SARS-CoV-2 infection **Key Exclusion Criteria:** • Patients with prolonged QTc intervals were excluded from HCQ arm. **Interventions:** • HCQ 800 mg at entry and at 6 hours, then HCQ 400 mg every 12 hours for 9 days or until discharge • Usual SOC **Primary Endpoint:** • All-cause mortality at Day 28 after randomization	**Number of Participants:** • HCQ (n = 1,561) and SOC (n = 3,155) • Study enrollment ended early after investigators and trial-steering committee concluded that the data showed no benefit for HCQ. **Participant Characteristics:** • Mean age was 65 years in both arms; 41% of patients were aged ≥70 years. • 90% of patients had laboratory-confirmed SARS-CoV-2 infection. • 57% of patients had ≥1 major comorbidity: 27% had diabetes mellitus, 26% had heart disease, and 22% had chronic lung disease. • At randomization, 17% of patients were receiving IMV or ECMO, 60% were receiving oxygen only (with or without noninvasive ventilation), and 24% were receiving neither. • Use of AZM or another macrolide during the follow-up period was similar in both arms, as was use of dexamethasone.	**Key Limitations:** • Not blinded • Information on occurrence of new major cardiac arrythmia was not collected throughout the trial. **Interpretation:** • HCQ does not decrease 28-day all-cause mortality when compared to the usual SOC in hospitalized patients with clinically suspected or laboratory-confirmed SARS-CoV-2 infection. • Patients who received HCQ had a longer median length of hospital stay, and those who were not on IMV at the time of randomization were more likely to require intubation or die during hospitalization if they received HCQ.

Study Design	Methods	Results	Limitations and Interpretation
RECOVERY Trial[22], continued			
		Outcomes: • No significant difference in 28-day mortality between the 2 arms; 421 patients (26.8%) in HCQ arm and 790 patients (27.0%) in SOC arm had died by Day 28 (rate ratio 1.09; 95% CI, 0.97–1.23; $P = 0.15$). • A similar 28-day mortality for HCQ patients was reported during the post hoc exploratory analysis that was restricted to the 4,266 participants (90.5%) who had a positive SARS-CoV-2 test result. • Patients in HCQ arm were less likely to survive hospitalization and had a longer median time to discharge than patients in SOC arm. • Patients who received HCQ and who were not on IMV at baseline had an increased risk of requiring intubation and an increased risk of death. • At the beginning of the study, the researchers did not record whether a patient developed a major cardiac arrhythmia after study enrollment; however, these data were later collected for 735 patients (47.1%) in HCQ arm and 1,421 patients (45.0%) in SOC arm. • No differences between the arms in the frequency of supraventricular tachycardia, ventricular tachycardia or fibrillation, or instances of AV block that required intervention; 1 case of Torsades de Pointes was reported in HCQ arm.	
Hydroxychloroquine and Hydroxychloroquine Plus Azithromycin for Mild or Moderate COVID-19[23]			
Open-label, 3-arm RCT in hospitalized adults (n = 667)	**Key Inclusion Criteria:** • Aged ≥18 years • Clinically suspected or laboratory-confirmed SARS-CoV-2 infection • Mild or moderate COVID-19 • Duration of symptoms ≤14 days	**Number of Participants:** • mITT analysis included patients with laboratory-confirmed SARS-CoV-2 infection (n = 504). **Participant Characteristics:** • Mean age was 50 years. • 58% of patients were men.	**Key Limitations:** • Not blinded • Follow-up period was restricted to 15 days. **Interpretation:** • Neither HCQ alone nor HCQ plus AZM improved clinical outcomes at Day 15 after randomization among hospitalized patients

Study Design	Methods	Results	Limitations and Interpretation
Hydroxychloroquine and Hydroxychloroquine Plus Azithromycin for Mild or Moderate COVID-19[23], continued			
	Key Exclusion Criteria: • Need for >4 L of supplemental oxygen or ≥40% FiO_2 by face mask • History of ventricular tachycardia • QT interval ≥480 ms **Interventions:** • HCQ 400 mg twice daily for 7 days plus SOC • HCQ 400 mg twice daily plus AZM 500 mg daily for 7 days plus SOC • SOC alone **Primary Endpoint:** • Clinical status at Day 15, as measured by a 7-point ordinal scale among the patients with confirmed SARS-CoV-2 infection **Ordinal Scale Definitions:** 1. Not hospitalized, no limitations 2. Not hospitalized, with limitations 3. Hospitalized, not on oxygen 4. Hospitalized, on oxygen 5. Hospitalized, oxygen administered by HFNC or noninvasive ventilation 6. Hospitalized, on mechanical ventilation 7. Death	• At baseline, 58.2% of patients were Ordinal Level 3; 41.8% were Ordinal Level 4. • Median time from symptom onset to randomization was 7 days. • 23.3% to 23.9% of patients received oseltamivir. **Outcomes:** • No significant difference in the odds of worse clinical status at Day 15 between patients in HCQ arm (OR 1.21; 95% CI, 0.69–2.11; $P = 1.00$) and patients in HCQ plus AZM arm (OR 0.99; 95% CI, 0.57–1.73; $P = 1.00$) • No significant differences in secondary outcomes of the 3 arms, including progression to mechanical ventilation during the first 15 days and mean number of days "alive and free of respiratory support" • A greater proportion of patients in HCQ plus AZM arm (39.3%) and HCQ arm (33.7%) experienced AEs than those in SOC arm (22.6%). • QT prolongation was more common in patients who received HCQ plus AZM or HCQ alone than in patients who received SOC alone, but fewer patients in SOC arm had serial electrocardiographic studies performed during the follow-up period.	with mild or moderate COVID-19.

Study Design	Methods	Results	Limitations and Interpretation
Hydroxychloroquine in Nonhospitalized Adults With Early COVID-19[24]			
Randomized, placebo-controlled trial in nonhospitalized adults (n = 491)	**Key Inclusion Criteria:** • Symptoms that were compatible with COVID-19 and lasted ≤4 days • Either laboratory-confirmed SARS-CoV-2 infection or high-risk exposure within the previous 14 days **Key Exclusion Criteria:** • Aged <18 years • Hospitalized • Receipt of certain medications **Interventions:** • HCQ 800 mg once, then HCQ 600 mg in 6–8 hours, then HCQ 600 mg once daily for 4 days • Placebo **Primary Endpoints:** • Planned primary endpoint was ordinal outcome by Day 14 in 4 categories: not hospitalized, hospitalized, ICU stay, or death. • Because event rates were lower than expected, a new primary endpoint was defined: change in overall symptom severity over 14 days, measured by a 10-point, self-reported, visual analogue scale	**Number of Participants:** • Contributed to primary endpoint data: HCQ (n = 212) and placebo (n = 211) **Participant Characteristics:** • 241 patients were exposed to people with COVID-19 through their position as health care workers (57%), 106 were exposed through household contacts (25%), and 76 had other types of exposure (18%). • Median age was 40 years. • 56% of patients were women. • Only 3% of patients were Black. • Very few patients had comorbidities: 11% had hypertension, 4% had diabetes, and 68% had no chronic medical conditions. • 56% of patients were enrolled on Day 1 of symptom onset. • 341 participants (81%) had either a positive PCR result or a high-risk exposure to a PCR-positive contact. **Outcomes:** • Compared to the placebo recipients, HCQ recipients had a nonsignificant 12% difference in improvement in symptoms between baseline and Day 14 (-2.60 vs. -2.33 points; $P = 0.117$). • Ongoing symptoms were reported by 24% of those in HCQ arm and 30% of those in the placebo arm at Day 14 ($P = 0.21$). • No difference in the incidence of hospitalization between the arms (4 patients in the HCQ arm vs. 10 patients in placebo arm); 2 of 10 placebo participants were hospitalized for reasons that were unrelated to COVID-19 • A higher percentage of patients in HCQ arm experienced AEs than patients in placebo arm (43% vs. 22%; $P < 0.001$).	**Key Limitations:** • This study enrolled a highly heterogeneous population. • Only 227 of 423 participants (53.7%) were confirmed PCR-positive for SARS-CoV-2. • Changing the primary endpoint without a new power calculation makes it difficult to assess whether the study is powered to detect differences in outcomes between the study arms. • This study used surveys for screening, symptom assessment, and adherence reporting. • Visual analogue scales are not commonly used, and their ability to assess acute viral respiratory infections in clinical trials has not been validated. **Interpretation:** • The study has some limitations, and it did not find evidence that early administration of HCQ reduced symptom severity in patients with mild COVID-19.

Study Design	Methods	Results	Limitations and Interpretation
Hydroxychloroquine in Nonhospitalized Adults With Mild COVID-19[25]			
Open-label RCT in nonhospitalized adults (n = 353)	**Key Inclusion Criteria:** • Laboratory-confirmed SARS-CoV-2 infection • <5 days of mild COVID-19 symptoms **Key Exclusion Criteria:** • Moderate to severe COVID-19 • Severe liver or renal disease • History of cardiac arrhythmia • QT prolongation **Interventions:** • HCQ 800 mg on Day 1, then HCQ 400 mg once daily for 6 days • No antiviral treatment (control arm) **Primary Endpoint:** • Reduction in SARS-CoV-2 viral load, assessed using NP swabs on Days 3 and 7 **Secondary Endpoints:** • Disease progression up to Day 28 • Time to complete resolution of symptoms	**Number of Participants:** • ITT analysis: HCQ (n = 136) and control (n = 157) • 60 patients were excluded from the ITT analysis due to negative baseline RT-PCR, missing RT-PCR at follow-up visits, or consent withdrawal. **Participant Characteristics:** • Mean age was 41.6 years. • 67% of patients were woman. • Majority of patients were health care workers (87%). • 53% of patients reported chronic health conditions. • Median time from symptom onset to enrollment was 3 days (IQR 2–4 days). • Most common COVID-19 symptoms were fever, cough, and sudden olfactory loss. **Outcomes:** • No significant difference in viral load reduction between control arm and HCQ arm at Day 3 • (-1.41 vs. -1.41 $\log_{10}$ copies/mL; difference of 0.01; 95% CI, -0.28 to 0.29), or at Day 7 (-3.37 vs. -3.44 $\log_{10}$ copies/mL; difference of -0.07; 95% CI, -0.44 to 0.29). • No difference in the risk of hospitalization between control arm and HCQ arm (7.1% vs. 5.9%; risk ratio 0.75; 95% CI, 0.32–1.77) • No difference in the median time from randomization to the resolution of COVID-19 symptoms between the 2 arms (12.0 days in control arm vs. 10.0 days in HCQ arm; $P = 0.38$) • A higher percentage of participants in the HCQ arm than in the control arm experienced AEs during the 28-day follow-up period (72% vs. 9%). Most common AEs were GI disorders and "nervous system disorders." • SAEs were reported in 12 patients in control arm and 8 patients in HCQ arm. SAEs that occurred among patients in HCQ arm were not deemed to be related to the drug.	**Key Limitations:** • Open-label, non-placebo-controlled trial • Study design allowed for the possibility of dropouts in control arm and over-reporting of AEs in HCQ arm. • The intervention changed during the study; the authors initially planned to include HCQ plus DRV/COBI. • The majority of the participants were relatively young health care workers. **Interpretation:** • Early administration of HCQ to patients with mild COVID-19 did not result in improvement in virologic clearance, a lower risk of disease progression, or a reduced time to symptom improvement.

Study Design	Methods	Results	Limitations and Interpretation
Observational Study on Hydroxychloroquine With or Without Azithromycin[26]			
Retrospective, multicenter, observational study in a random sample of hospitalized adults with COVID-19 from the New York Department of Health (n = 1,438)	**Key Inclusion Criteria:** • Laboratory-confirmed SARS-CoV-2 infection **Interventions:** • HCQ plus AZM • HCQ alone • AZM alone • Neither drug **Primary Endpoint:** • In-hospital mortality **Secondary Endpoint:** • Cardiac arrest and arrhythmia or QT prolongation on an ECG	**Number of Participants:** • HCQ plus AZM (n = 735), HCQ alone (n = 271), AZM alone (n = 211), and neither drug (n = 221) **Participant Characteristics:** • Patients in the treatment arms had more severe disease at baseline than those who received neither drug. **Outcomes:** • In adjusted analyses, patients who received 1 of the 3 treatment regimens did not show a decreased in-hospital mortality rate when compared with those who received neither drug. • Patients who received HCQ plus AZM had a greater risk of cardiac arrest than patients who received neither drug (OR 2.13; 95% CI, 1.12–4.05).	**Key Limitations:** • This study has the inherent limitations of an observational study, including residual confounding from confounding variables that were unrecognized and/or unavailable for analysis. **Interpretation:** • Despite the limitations discussed above, these findings suggest that although HCQ and AZM are not associated with an increased risk of in-hospital death, the combination of HCQ and AZM may be associated with an increased risk of cardiac arrest.
Observational Study of Hydroxychloroquine Versus No Hydroxychloroquine in New York City[27]			
Observational study in hospitalized adults with COVID-19 at a large medical center (n = 1,376)	**Key Inclusion Criteria:** • Laboratory-confirmed SARS-CoV-2 infection **Key Exclusion Criteria:** • Intubation, death, or transfer to another facility within 24 hours of arriving at the emergency department **Interventions:** • HCQ 600 mg twice daily on Day 1, then HCQ 400 mg once daily for 4 days • No HCQ **Primary Endpoint:** • Time from study baseline (24 hours after patients arrived at the ED) to intubation or death	**Number of Participants:** • Received HCQ (n = 811) and did not receive HCQ (n = 565) **Participant Characteristics:** • HCQ recipients were more severely ill at baseline than those who did not receive HCQ. **Outcomes:** • Using propensity scores to adjust for major predictors of respiratory failure and inverse probability weighting, the study demonstrated that HCQ use was not associated with intubation or death (HR 1.04; 95% CI, 0.82–1.32). • No association between concomitant use of AZM and the composite endpoint of intubation or death (HR 1.03; 95% CI, 0.81–1.31)	**Key Limitations:** • This study has the inherent limitations of an observational study, including residual confounding from confounding variables that were unrecognized and/or unavailable for analysis. **Interpretation:** • The use of HCQ for treatment of COVID-19 was not associated with harm or benefit in a large observational study.

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

References

1. Chorin E, Dai M, Shulman E, et al. The QT interval in patients with COVID-19 treated with hydroxychloroquine and azithromycin. *Nat Med*. 2020;26(6):808-809. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32488217.
2. Gautret P, Lagier JC, Parola P, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study. *Travel Med Infect Dis*. 2020:101663. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32289548.
3. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents*. 2020:105949. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32205204.
4. Huang M, Tang T, Pang P, et al. Treating COVID-19 with chloroquine. *J Mol Cell Biol*. 2020;12(4):322-325. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32236562.
5. Magagnoli J, Narendran S, Pereira F, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with COVID-19. *Med (N Y)*. 2020;1(1):114-127.e3. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32838355.
6. Molina JM, Delaugerre C, Le Goff J, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. *Med Mal Infect*. 2020;50(4):384. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32240719.
7. Satlin MJ, Goyal P, Magleby R, et al. Safety, tolerability, and clinical outcomes of hydroxychloroquine for hospitalized patients with coronavirus 2019 disease. *PLoS One*. 2020;15(7):e0236778. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32701969.
8. Mikami T, Miyashita H, Yamada T, et al. Risk factors for mortality in patients with COVID-19 in New York City. *J Gen Intern Med*. 2021;36(1):17-26. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32607928.
9. Catteau L, Dauby N, Montourcy M, et al. Low-dose hydroxychloroquine therapy and mortality in hospitalised patients with COVID-19: a nationwide observational study of 8075 participants. *Int J Antimicrob Agents*. 2020:106144. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32853673.
10. COVID-19 RISK and Treatments (CORIST) Collaboration. Use of hydroxychloroquine in hospitalised COVID-19 patients is associated with reduced mortality: findings from the observational multicentre Italian CORIST study. *Eur J Intern Med*. 2020;82:38-47. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32859477.
11. Furtado RHM, Berwanger O, Fonseca HA, et al. Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial. *Lancet*. 2020;396(10256):959-967. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32896292.
12. Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised

controlled trial. *BMJ*. 2020;369:m1849. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32409561.

13. Borba MGS, Val FFA, Sampaio VS, et al. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial. *JAMA Netw Open*. 2020;3(4):e208857. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32339248.
14. Mahevas M, Tran VT, Roumier M, et al. Clinical efficacy of hydroxychloroquine in patients with COVID-19 pneumonia who require oxygen: observational comparative study using routine care data. *BMJ*. 2020;369:m1844. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32409486.
15. Arshad S, Kilgore P, Chaudhry ZS, et al. Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. *Int J Infect Dis*. 2020;97:396-403. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32623082.
16. Recovery Collaborative Group. Azithromycin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. 2021;397(10274):605-612. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33545096.
17. Omrani AS, Pathan SA, Thomas SA, et al. Randomized double-blinded placebo-controlled trial of hydroxychloroquine with or without azithromycin for virologic cure of non-severe COVID-19. *EClinicalMedicine*. 2020;29:100645. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33251500.
18. Principle Trial Collaborative Group. Azithromycin for community treatment of suspected COVID-19 in people at increased risk of an adverse clinical course in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. *Lancet*. 2021;397(10279):1063-1074. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33676597.
19. Hinks TSC, Cureton L, Knight R, et al. A randomised clinical trial of azithromycin versus standard care in ambulatory COVID-19–the ATOMIC2 trial. *medRxiv*. 2021;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.04.21.21255807v1.
20. WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed antiviral drugs for COVID-19—interim WHO Solidarity Trial results. *N Engl J Med*. 2021;384(6):497-511. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33264556.
21. Self WH, Semler MW, Leither LM, et al. Effect of hydroxychloroquine on clinical status at 14 days in hospitalized patients with COVID-19: a randomized clinical trial. *JAMA*. 2020;324(21):2165-2176. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33165621.
22. Recovery Collaborative Group, Horby P, Mafham M, et al. Effect of hydroxychloroquine in hospitalized patients with COVID-19. *N Engl J Med*. 2020;383(21):2030-2040. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33031652.
23. Cavalcanti AB, Zampieri FG, Rosa RG, et al. Hydroxychloroquine with or without azithromycin in mild-to-moderate COVID-19. *N Engl J Med*. 2020;383(21):2041-2052. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32706953.
24. Skipper CP, Pastick KA, Engen NW, et al. Hydroxychloroquine in nonhospitalized adults with early COVID-19: a randomized trial. *Ann Intern Med*. 2020;173(8):623-631. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32673060.
25. Mitja O, Corbacho-Monne M, Ubals M, et al. Hydroxychloroquine for early treatment of adults with mild COVID-19: a randomized-controlled trial. *Clin Infect Dis*. 2020;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32674126.
26. Rosenberg ES, Dufort EM, Udo T, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York state. *JAMA*. 2020;323(24):2493-2502. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32392282.
27. Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with COVID-19. *N Engl J Med*. 2020;382(25):2411-2418. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32379955.

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 2c).

Clinical Trials

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

Adverse Effects

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

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.

References

1. Alavi Darazam I, Hatami F, Mahdi Rabiei M, et al. An investigation into the beneficial effects of high-dose interferon beta 1-a, compared to low-dose interferon beta 1-a in severe COVID-19: The COVIFERON II randomized controlled trial. *Int Immunopharmacol*. 2021;99:107916. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34224994.
2. Hung IF, Lung KC, Tso EY, et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, Phase 2 trial. *Lancet*. 2020;395(10238):1695-1704. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32401715.
3. Rahmani H, Davoudi-Monfared E, Nourian A, et al. Interferon beta-1b in treatment of severe COVID-19: a randomized clinical trial. *Int Immunopharmacol*. 2020;88:106903. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32862111.
4. Kalil AC, Mehta AK, Patterson TF, et al. Efficacy of interferon beta-1a plus remdesivir compared with remdesivir alone in hospitalised adults with COVID-19: a double-bind, randomised, placebo-controlled, Phase 3 trial. *Lancet Respir Med*. 2021;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34672949.
5. WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed antiviral drugs for COVID-19—interim WHO Solidarity Trial results. *N Engl J Med*. 2021;384(6):497-511. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33264556.
6. Interferon alfa-2b (Intron A) [package insert]. Food and Drug Administration. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103132Orig1s5199lbl.pdf.
7. Interferon beta-1a (Rebif) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/103780s5204lbl.pdf.
8. Sandberg-Wollheim M, Alteri E, Moraga MS, Kornmann G. Pregnancy outcomes in multiple sclerosis following subcutaneous interferon beta-1a therapy. *Mult Scler*. 2011;17(4):423-430. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21220368.
9. Hellwig K, Duarte Caron F, Wicklein EM, Bhatti A, Adamo A. Pregnancy outcomes from the global pharmacovigilance database on interferon beta-1b exposure. *Ther Adv Neurol Disord*. 2020;13:1756286420910310. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32201504.
10. Burkill S, Vattulainen P, Geissbuehler Y, et al. The association between exposure to interferon-beta during pregnancy and birth measurements in offspring of women with multiple sclerosis. *PLoS One*. 2019;14(12):e0227120. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31887199.

Table 2c. Interferons: Selected Clinical Data

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

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

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

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

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

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

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

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

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

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

References

1. Kalil AC, Mehta AK, Patterson TF, et al. Efficacy of interferon beta-1a plus remdesivir compared with remdesivir alone in hospitalised adults with COVID-19: a double-bind, randomised, placebo-controlled, Phase 3 trial. *Lancet Respir Med*. 2021;9(12):1365-1376. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34672949.
2. WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed antiviral drugs for COVID-19—interim WHO Solidarity Trial results. *N Engl J Med*. 2021;384(6):497-511. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33264556.
3. Ader F, Peiffer-Smadja N, Poissy J, et al. An open-label randomized controlled trial of the effect of lopinavir/ritonavir, lopinavir/ritonavir plus

IFN-beta-1a and hydroxychloroquine in hospitalized patients with COVID-19. *Clin Microbiol Infect*. 2021;27(12):1826-1837. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34048876.

4. Jagannathan P, Andrews JR, Bonilla H, et al. Peginterferon lambda-1a for treatment of outpatients with uncomplicated COVID-19: a randomized placebo-controlled trial. *Nat Commun*. 2021;12(1):1967. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33785743.
5. Feld JJ, Kandel C, Biondi MJ, et al. Peginterferon lambda for the treatment of outpatients with COVID-19: a Phase 2, placebo-controlled randomised trial. *Lancet Respir Med*. 2021;9(5):498-510. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33556319.

Ivermectin

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

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

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

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

Recommendation

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

Rationale

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

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

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

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

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

Monitoring, Adverse Effects, and Drug-Drug Interactions

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

Considerations in Pregnancy

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

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

Considerations in Children

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

Clinical Trials

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

References

1. Omura S, Crump A. Ivermectin: panacea for resource-poor communities? *Trends Parasitol*. 2014;30(9):445-455. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25130507.
2. Fritz ML, Siegert PY, Walker ED, Bayoh MN, Vulule JR, Miller JR. Toxicity of bloodmeals from ivermectin-treated cattle to Anopheles gambiae s.l. *Ann Trop Med Parasitol*. 2009;103(6):539-547. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19695159.
3. Kircik LH, Del Rosso JQ, Layton AM, Schauber J. Over 25 years of clinical experience with ivermectin: an overview of safety for an increasing number of indications. *J Drugs Dermatol*. 2016;15(3):325-332. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26954318.
4. Yang SNY, Atkinson SC, Wang C, et al. The broad spectrum antiviral ivermectin targets the host nuclear transport importin alpha/beta1 heterodimer. *Antiviral Res*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32135219.
5. Arévalo AP, Pagotto R, Pórfido J, et al. Ivermectin reduces coronavirus infection in vivo: a mouse experimental model. *bioRxiv*. 2020;Preprint. Available at: https://www.biorxiv.org/content/10.1101/2020.11.02.363242v1.
6. Lehrer S, Rheinstein PH. Ivermectin docks to the SARS-CoV-2 spike receptor-binding domain attached to ACE2. *In Vivo*. 2020;34(5):3023-3026. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32871846.
7. Tay MY, Fraser JE, Chan WK, et al. Nuclear localization of dengue virus (DENV) 1-4 non-structural protein 5; protection against all 4 DENV serotypes by the inhibitor ivermectin. *Antiviral Res*. 2013;99(3):301-306. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23769930.
8. Wagstaff KM, Sivakumaran H, Heaton SM, Harrich D, Jans DA. Ivermectin is a specific inhibitor of importin alpha/beta-mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. *Biochem J*. 2012;443(3):851-856. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22417684.
9. Barrows NJ, Campos RK, Powell ST, et al. A screen of FDA-approved drugs for inhibitors of Zika virus infection. *Cell Host Microbe*. 2016;20(2):259-270. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27476412.
10. Zhang X, Song Y, Ci X, et al. Ivermectin inhibits LPS-induced production of inflammatory cytokines and improves LPS-induced survival in mice. *Inflamm Res*. 2008;57(11):524-529. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19109745.
11. DiNicolantonio JJ, Barroso J, McCarty M. Ivermectin may be a clinically useful anti-inflammatory agent for late-stage COVID-19. *Open Heart*. 2020;7(2). Available at: https://www.ncbi.nlm.nih.gov/pubmed/32895293.
12. Ci X, Li H, Yu Q, et al. Avermectin exerts anti-inflammatory effect by downregulating the nuclear transcription factor kappa-B and mitogen-activated protein kinase activation pathway. *Fundam Clin Pharmacol*. 2009;23(4):449-455. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19453757.
13. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the

replication of SARS-CoV-2 in vitro. *Antiviral Res*. 2020;178:104787. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32251768.

14. Chaccour C, Hammann F, Ramon-Garcia S, Rabinovich NR. Ivermectin and COVID-19: keeping rigor in times of urgency. *Am J Trop Med Hyg*. 2020;102(6):1156-1157. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32314704.
15. Guzzo CA, Furtek CI, Porras AG, et al. Safety, tolerability, and pharmacokinetics of escalating high doses of ivermectin in healthy adult subjects. *J Clin Pharmacol*. 2002;42(10):1122-1133. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12362927.
16. Arshad U, Pertinez H, Box H, et al. Prioritization of anti-SARS-CoV-2 drug repurposing opportunities based on plasma and target site concentrations derived from their established human pharmacokinetics. *Clin Pharmacol Ther*. 2020;108(4):775-790. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32438446.
17. Bray M, Rayner C, Noel F, Jans D, Wagstaff K. Ivermectin and COVID-19: a report in antiviral research, widespread interest, an FDA warning, two letters to the editor and the authors' responses. *Antiviral Res*. 2020;178:104805. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32330482.
18. Momekov G, Momekova D. Ivermectin as a potential COVID-19 treatment from the pharmacokinetic point of view: antiviral levels are not likely attainable with known dosing regimens. *Biotechnology & Biotechnological Equipment*. 2020;34(1):469-474. Available at: https://www.tandfonline.com/doi/full/10.1080/13102818.2020.1775118.
19. Jermain B, Hanafin PO, Cao Y, Lifschitz A, Lanusse C, Rao GG. Development of a minimal physiologically-based pharmacokinetic model to simulate lung exposure in humans following oral administration of ivermectin for COVID-19 drug repurposing. *J Pharm Sci*. 2020;109(12):3574-3578. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32891630.
20. de Melo GD, Lazarini F, Larrous F, et al. Anti-COVID-19 efficacy of ivermectin in the golden hamster. *bioRxiv*. 2020;Preprint. Available at: https://www.biorxiv.org/content/10.1101/2020.11.21.392639v1.
21. Ahmed S, Karim MM, Ross AG, et al. A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. *Int J Infect Dis*. 2020;103:214-216. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33278625.
22. Chachar AZK, Khan KA, Asif M, Tanveer K, Khaqan A, Basri R. Effectiveness of ivermectin in SARS-COV-2/COVID-19 Patients. *Int J of Sci*. 2020;9:31-35. Available at: https://www.ijsciences.com/pub/article/2378.
23. Chowdhury ATMM, Shahbaz M, Karim MR, Islam J, Guo D, He S. A randomized trial of ivermectin-doxycycline and hydroxychloroquine-azithromycin therapy on COVID19 patients. *Research Square*. 2020;Preprint. Available at: https://assets.researchsquare.com/files/rs-38896/v1/3ee350c3-9d3f-4253-85f9-1f17f3af9551.pdf.
24. Soto-Becerra P, Culquichicón C, Hurtado-Roca Y, Araujo-Castillo RV. Real-world effectiveness of hydroxychloroquine, azithromycin, and ivermectin among hospitalized COVID-19 patients: results of a target trial emulation using observational data from a nationwide healthcare system in Peru. *medRxiv*. 2020;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2020.10.06.20208066v3.
25. Hashim HA, Maulood MF, Rasheed AW, Fatak DF, Kabah KK, Abdulamir AS. Controlled randomized clinical trial on using ivermectin with doxycycline for treating COVID-19 patients in Baghdad, Iraq. *medRxiv*. 2020;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2020.10.26.20219345v1/.
26. Niaee MS, Gheibi N, Namdar P, et al. Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: a randomized multi-center clinical trial. *Research Square*. 2020;Preprint. Available at: https://www.researchsquare.com/article/rs-109670/v1.
27. Khan MSI, Khan MSI, Debnath CR, et al. Ivermectin treatment may improve the prognosis of patients with COVID-19. *Arch Bronconeumol*. 2020;56(12):828-830. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33293006.

28. Chandler RE. Serious neurological adverse events after ivermectin—do they occur beyond the indication of onchocerciasis? *Am J Trop Med Hyg*. 2018;98(2):382-388. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29210346.

29. Ivermectin [package insert]. *DailyMed*. 2017. Available at: https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=847a1dd7-d65b-4a0e-a67d-d90392059dac&type=display.

30. Pacque M, Munoz B, Poetschke G, Foose J, Greene BM, Taylor HR. Pregnancy outcome after inadvertent ivermectin treatment during community-based distribution. *Lancet*. 1990;336(8729):1486-1489. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1979100.

31. Chippaux JP, Gardon-Wendel N, Gardon J, Ernould JC. Absence of any adverse effect of inadvertent ivermectin treatment during pregnancy. *Trans R Soc Trop Med Hyg*. 1993;87(3):318. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8236406.

32. Gyapong JO, Chinbuah MA, Gyapong M. Inadvertent exposure of pregnant women to ivermectin and albendazole during mass drug administration for lymphatic filariasis. *Trop Med Int Health*. 2003;8(12):1093-1101. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14641844.

Table 2d. Ivermectin: Selected Clinical Data

Last Updated: December 16, 2021

The Panel has reviewed other clinical studies of IVM for the treatment of COVID-19.[1-25] However, those studies have limitations that make them less definitive and informative than the studies discussed below. 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
IVERCOR-COVID19: Double-Blind, Placebo-Controlled RCT of Ivermectin to Prevent Hospitalizations in Patients With COVID-19 in Argentina[26]		
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 doses of IVM given 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	**Participant Characteristics:** • Mean age 42 years; 8% aged ≥65 years • 47% were women • 24% with HTN; 10% with DM; 58% with ≥1 comorbidity • Median time from symptom onset was 4 days **Primary Outcome:** • COVID-19-related hospitalizations: 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 deaths: 2% in IVM arm vs. 1% in placebo arm (P = 0.7) • AEs: 18% in IVM arm vs. 21% in placebo arm (P = 0.6)	**Key Limitation:** • Study enrolled a fairly young population with few comorbidities that predict disease progression **Interpretation:** • In patients who had recently acquired SARS-CoV-2 infection, there was no evidence of a clinical benefit for IVM.

Methods	Results	Limitations and Interpretation
Double-Blind, Placebo-Controlled RCT of Ivermectin for Treatment of Mild COVID-19 in Columbia[27]		
Key Inclusion Criteria: • Positive SARS-CoV-2 PCR or antigen test result • Symptoms for ≤7 days • Mild disease **Key Exclusion Criteria:** • Asymptomatic disease • Severe pneumonia • Hepatic dysfunction **Interventions:** • IVM 300 µg/kg per day for 5 days (n = 200) • Placebo (n = 198) **Primary Endpoint:** • Time to resolution of symptoms within 21 days **Key Secondary Endpoints:** • Proportion of patients with clinical deterioration • Proportion of patients who required escalation in care	**Participant Characteristics:** • Median age 37 years; 4% in IVM arm and 8% in placebo arm aged ≥65 years • 39% in IVM arm and 45% in placebo arm were men • 79% had no known comorbidities • Median of 5 days from symptom onset to randomization **Primary Outcomes:** • 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:** • No difference between arms in proportion of patients who had clinical deterioration or who required escalation in care. **Safety Outcomes:** • Discontinued treatment due to an AE: 8% in IVM arm vs. 3% in placebo arm • No SAEs were considered to be related to study interventions.	**Key Limitations:** • Primary endpoint changed from proportion of patients with clinical deterioration to time to symptom resolution during the trial due to low event rates • Study enrolled younger, healthier patients; this population does not typically develop severe COVID-19 **Interpretation:** • A 5-day course of IVM 300 µg/kg per day did not improve the time to resolution of symptoms in patients with mild COVID-19.

Methods	Results	Limitations and Interpretation
Open-Label RCT of Ivermectin Plus Doxycycline Versus Hydroxychloroquine Plus Azithromycin for Asymptomatic Patients and Patients With Mild to Moderate COVID-19 in Bangladesh[28]		
Key Inclusion Criteria: • Aged 16–80 years • PCR-confirmed SARS-CoV-2 infection • SpO_2 ≥95% • Normal or near-normal CXR • No unstable comorbidities **Interventions:** • Single dose of IVM 200 µg/kg plus DOX 100 mg twice daily for 10 days (n = 60) • HCQ 400 mg on Day 1, then HCQ 200 mg twice daily for 9 days plus AZM 500 mg once daily for 5 days (n = 56) **Primary Endpoints:** • Time to negative PCR result • Time to resolution of symptoms	**Participant Characteristics:** • Mean age 34 years; 78% were men • 78% were symptomatic at baseline **Primary Outcomes:** • Mean time to negative PCR result: 9 days in both arms • In patients who were symptomatic at baseline, mean time to negative PCR result: 9 days in IVM/DOX arm vs. 10 days in HCQ/AZM arm ($P = 0.07$) • Mean time to symptom recovery: 6 days in IVM/DOX arm vs. 7 days in HCQ/AZM arm ($P = 0.07$) • Patients who received IVM/DOX had fewer AEs than those who received HCQ/AZM (32% vs. 46%).	**Key Limitations:** • Small sample size • Open-label study • No SOC alone group • Study enrolled young patients who were not at high risk for disease progression **Interpretation:** • There was no difference in the time to a negative SARS-CoV-2 PCR result or symptom recovery between patients who received IVM plus DOX and those who received HCQ plus AZM.
Double-Blind, Placebo-Controlled RCT of Ivermectin for Treatment of Mild to Moderate COVID-19 in India[29]		
Key Inclusion Criteria: • Positive SARS-CoV-2 RT-PCR or antigen test result • Hospitalized with mild or moderate COVID-19 **Interventions:** • IVM 12 mg for 2 days (n = 55) • Placebo (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 • Mortality	**Participant Characteristics:** • Mean age 53 years; 28% were women • 35% with HTN; 36% with DM • 79% with mild COVID-19 • Mean of 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; $P = 0.36$)	**Key Limitations:** • The primary endpoint of the study was a negative SARS-CoV-2 RT-PCR result on Day 6. However, the study reported no RT-PCR result or an inconclusive RT-PCR result for 42% of patients in the IVM arm and 23% in the placebo arm. • Time to discharge was not reported and outcomes after discharge were not evaluated **Interpretation:** • There was no significant virologic or clinical benefit of IVM for patients with mild to moderate COVID-19.

Methods	Results	Limitations and Interpretation
Double-Blind, Placebo-Controlled RCT of Ivermectin for Treatment of Mild to Moderate COVID-19 in India[29], continued		
	• Discharge by Day 10: 80% in IVM arm vs. 74% in placebo arm (RR 1.1; *P* = 0.43) • No difference between arms in proportion of patients who were admitted to ICU or who required MV. • Inpatient deaths: 0 in IVM arm (0%) vs. 4 in placebo arm (7%)	
RIVET-COV: Double-Blind, Placebo-Controlled RCT of Ivermectin in Patients With Mild to Moderate COVID-19 in India[30]		
Key Inclusion Criteria: • Positive SARS-CoV-2 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 (n = 51) • Single dose of IVM 12 mg (n = 49) • Placebo (n = 52) **Primary Endpoints:** • Reduction of SARS-CoV-2 VL at Day 5 • Negative PCR result at Day 5 **Key Secondary Endpoints:** • Time to symptom resolution • Clinical status at Day 14 • Number of hospital-free days at Day 28	**Participant Characteristics:** • Mean age 35 years; 89% were men • 60% to 68% had mild COVID-19 (including asymptomatic patients); 33% to 40% had moderate COVID-19 • Median duration of symptoms was similar between arms (4–5 days). • 10% received concurrent antivirals (RDV, favipiravir, or HCQ); no difference between arms. **Primary Outcomes:** • Proportion with negative PCR result on Day 5: 48% in IVM 24 mg arm vs. 35% in IVM 12 mg arm vs. 31% in placebo arm (*P* = 0.30) • VL at enrollment did not impact conversion to negative RT-PCR on Day 5. • No significant difference between arms in VL decline by Day 5. **Secondary Outcomes:** • No difference between arms in time to symptom resolution or number of hospital-free days at Day 28. • Proportion with clinical worsening similar across arms: 8% in IVM 24 mg arm vs. 5% in IVM 12 mg arm vs. 11% in placebo arm (*P* = 0.65) • No difference between arms in frequency of AEs. • No SAEs reported.	**Key Limitation:** • Small sample size **Interpretation:** • There was no difference in the rate of negative PCR results on Day 5 or clinical outcomes between patients who received IVM and those who received placebo.

Methods	Results	Limitations and Interpretation
Double-Blind RCT of Ivermectin, Chloroquine, or Hydroxychloroquine in Hospitalized Adults With Severe COVID-19 in Brazil[31]		

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 on 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
• Mortality
	Participant Characteristics:
	• Mean age 53 years; 58% were men
	• Most common comorbidities: HTN (43%); DM (28%); BMI >30 (38%)
	• 76% had respiratory failure on admission
	Outcomes:
	• No difference between IVM, CQ, and HCQ arms in:
	  • Proportion requiring 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
	• No difference in proportion of patients with AEs between the arms.
	• Baseline characteristics that were 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 placebo control
		• 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 required supplemental oxygen, ICU admission, or MV or the proportion of patients who died.

Methods	Results	Limitations and Interpretation
Double-Blind RCT of Ivermectin as Adjunctive Therapy in Hospitalized Patients With Mild to Severe COVID-19 in Iran[32]		

Key Inclusion Criterion:
• Symptoms suggestive of COVID-19 pneumonia, with compatible chest CT scan or positive SARS-CoV-2 PCR result
Key Exclusion Criterion:
• Severe immunosuppression, malignancy, or chronic kidney disease
Interventions:
• HCQ 200 mg twice daily as SOC plus 1 of the following:
  • SOC alone (n = 30)
  • Placebo (n = 30)
  • Single dose of IVM 200 µg/kg (n = 30)
  • IVM 200 µg/kg on Days 1, 3, and 5 (n = 30)
  • Single dose of IVM 400 µg/kg (n = 30)
  • IVM 400 µg/kg on Day 1, then IVM 200 µg/kg on Days 3 and 5 (n = 30)
Primary Endpoints:
• Clinical recovery
• All-cause mortality
	Participant Characteristics:
	• Median age 53–61 years across arms; 50% were men
	• Disease severity stratification (based on CT findings): negative (1%), mild (14%), moderate (73%), severe (12%)
	• Median SpO_2 at baseline was 88% to 91% across arms
	• Proportion of patients in each arm with a positive SARS-CoV-2 PCR result varied, with a range of 47% to 97%
	Primary Outcomes:
	• Median duration of hypoxemia was shorter in IVM arms than in placebo arm ($P = 0.025$).
	• Median duration of hospitalization was shorter in IVM arms than in placebo arm ($P = 0.006$).
	• No difference between the arms in number of days of tachypnea or number of days to return to normal temperature.
	• Mortality was higher in SOC and placebo arms (18%) than in IVM arms (3%; $P < 0.001$).
		Key Limitations:
		• Since IVM was given as a single dose or multiple doses and no placebo was given to patients in these arms, the study was not truly blinded
		• Large proportion of patients did not have laboratory-confirmed SARS-CoV-2 infection, and there was an imbalance across arms in the proportion of patients with laboratory-confirmed SARS-CoV-2 infection
		• Concerns have been raised about whether the study was conducted as reported[33]
		• Post hoc grouping of randomized arms raises risk of false positive findings
		Interpretation:
		• The unclear treatment arm assignments and the lack of accounting for disease severity at baseline make it difficult to draw conclusions about the efficacy of using IVM to treat mild COVID-19.

Key: AE = adverse event; AZM = azithromycin; BMI = body mass index; CQ = chloroquine; CrCl = creatinine clearance; CT = computed tomography; CXR = chest X-ray; DM = diabetes mellitus; DOX = doxycycline; HCQ = hydroxychloroquine; HTN = hypertension; ICU = intensive care unit; IVM = ivermectin; MI = myocardial infarction; 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; PCR = polymerase chain reaction; 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

References

1. Spoorthi V, Sasank S. Utility of ivermectin and doxycycline combination for the treatment of SARS-CoV-2. *International Archives of Integrated Medicine*. 2020;7(10):117-182. Available at: https://iaimjournal.com/wp-content/uploads/2020/10/iaim_2020_0710_23.pdf.
2. Camprubi D, Almuedo-Riera A, Marti-Soler H, et al. Lack of efficacy of standard doses of ivermectin in severe COVID-19 patients. *PLoS One*. 2020;15(11):e0242184. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33175880.
3. Bhattacharya R, Ray I, Mukherjee R, et al. Observational study on clinical features, treatment and outcome of COVID-19 in a tertiary care centre in India—a restrospective case series. *International Journal of Scientific Research*. 2020;9(10). Available at: https://www.worldwidejournals.com/international-journal-of-scientific-research-(IJSR)/article/observational-study-on-clinical-features-treatment-and-outcome-of-covid-19-in-a-tertiary-care-centre-in-india-andndash-a-retrospective-case-series/MzI0NTg=/?is=1&b1=141&k=36.
4. Morgenstern J, Redondo JN, De León A, et al. The use of compassionate ivermectin in the management of symptomatic outpatients and hospitalized patients with clinical diagnosis of COVID-19 at the Medical Center Bournigal and the Medical Center Punta Cana, Rescue Group, Dominican Republic, from May 1 to August 10, 2020. *medRxiv*. 2020;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2020.10.29.20222505v1.
5. Cadegiani FA, Goren A, Wambier CG, McCoy J. Early COVID-19 therapy with azithromycin plus nitazoxanide, ivermectin or hydroxychloroquine in outpatient settings significantly improved COVID-19 outcomes compared to known outcomes in untreated patients. *New Microbes New Infect*. 2021;43:100915. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34249367.
6. Carvallo H, Roberto H, Eugenia FM. Safety and efficacy of the combined use of ivermectin, dexamethasone, enoxaparin and aspirin against COVID 19. *medRxiv*. 2020;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2020.09.10.20191619v1.
7. Bukhari KHS, Asghar A, Perveen N, et al. Efficacy of ivermectin in COVID-19 patients with mild to moderate disease. *medRxiv*. 2021;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.02.02.21250840v1.
8. Elalfy H, Besheer T, El-Mesery A, et al. Effect of a combination of nitazoxanide, ribavirin, and ivermectin plus zinc supplement (MANS.NRIZ study) on the clearance of mild COVID-19. *J Med Virol*. 2021;93(5):3176-3183. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33590901.
9. Chahla RE, Ruiz LM, Mena T, et al. Cluster randomised trials—ivermectin repurposing for COVID-19 treatment of outpatients with mild disease in primary health care centers. *Research Square*. 2021;Preprint. Available at: https://www.researchsquare.com/article/rs-495945/v1.
10. Tanioka H, Tanioka S, Kaga K. Why COVID-19 is not so spread in Africa: how does ivermectin affect it? *medRxiv*. 2021;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.03.26.21254377v1.
11. Roy S, Samajdar SS, Tripathi SK, Mukherjee S, Bhattacharjee K. Outcome of different therapeutic interventions in mild COVID-19 patients in a single OPD clinic of West Bengal: a retrospective study. *medRxiv*. 2021;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.03.08.21252883v2.
12. Pott-Junior H, Paoliello MMB, Miguel AQC, et al. Use of ivermectin in the treatment of COVID-19: a pilot trial. *Toxicol Rep*. 2021;8:505-510. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33723507.
13. Shahbaznejad L, Davoudi A, Eslami G, et al. Effects of ivermectin in patients with COVID-19: a multicenter, double-blind, randomized, controlled clinical trial. *Clin Ther*. 2021;43(6):1007-1019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34052007.
14. Roman YM, Burela PA, Pasupuleti V, et al. Ivermectin for the treatment of COVID-19: a systematic review and meta-analysis of randomized controlled trials. *Clin Infect Dis*. 2021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34181716.

15. Ahmed S, Karim MM, Ross AG, et al. A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. *Int J Infect Dis*. 2021;103:214-216. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33278625.

16. Chaccour C, Casellas A, Blanco-Di Matteo A, et al. The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with non-severe COVID-19: a pilot, double-blind, placebo-controlled, randomized clinical trial. *EClinicalMedicine*. 2021;32:100720. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33495752.

17. Chachar AZK, Khan KA, Asif M, et al. Effectiveness of ivermectin in SARS-COV-2/COVID-19 patients. *Int J of Sci*. 2020;9:31-35. Available at: https://www.ijsciences.com/pub/article/2378.

18. Gonzalez JLB, Gámez MG, Enciso EAM, et al. Efficacy and safety of ivermectin and hydroxychloroquine in patients with severe COVID-19. *medRxiv*. 2020;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.02.18.21252037v1.

19. Hashim HA, Maulood MF, Rasheed AW, et al. Controlled randomized clinical trial on using ivermectin with doxycycline for treating COVID-19 patients in Baghdad, Iraq. *medRxiv*. 2020;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2020.10.26.20219345v1/.

20. Khan MSI, Khan MSI, Debnath CR, et al. Ivermectin treatment may improve the prognosis of patients with COVID-19. *Arch Bronconeumol (Engl Ed)*. 2020;56(12):828-830. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33293006.

21. Krolewiecki A, Lifschitz A, Moragas M, et al. Antiviral effect of high-dose ivermectin in adults with COVID-19: a proof-of-concept randomized trial. *EClinicalMedicine*. 2021;37:100959. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34189446.

22. Okumus N, Demirturk N, Cetinkaya RA, et al. Evaluation of the effectiveness and safety of adding ivermectin to treatment in severe COVID-19 patients. *BMC Infect Dis*. 2021;21(1):411. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33947344.

23. Podder CS, Chowdhury N, Sina MI, Haque W. Outcome of ivermectin treated mild to moderate COVID-19 cases: a single-centre, open-label, randomised controlled study. *IMC Journal of Medical Science*. 2021. Available at: https://doi.org/10.3329/imcjms.v14i2.52826.

24. Soto-Becerra P, Culquichicón C, Hurtado-Roca Y, Araujo-Castillo RV. Real-world effectiveness of hydroxychloroquine, azithromycin, and ivermectin among hospitalized COVID-19 patients: results of a target trial emulation using observational data from a nationwide healthcare system in Peru. *medRxiv*. 2020;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2020.10.06.20208066v3.

25. Rajter JC, Sherman MS, Fatteh N, et al. Use of ivermectin is associated with lower mortality in hospitalized patients with coronavirus disease 2019: the ivermectin in COVID nineteen study. *Chest*. 2021;159(1):85-92. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33065103.

26. Vallejos J, Zoni R, Bangher M, et al. Ivermectin to prevent hospitalizations in patients with COVID-19 (IVERCOR-COVID19) a randomized, double-blind, placebo-controlled trial. *BMC Infect Dis*. 2021;21(1):635. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34215210.

27. Lopez-Medina E, Lopez P, Hurtado IC, et al. Effect of ivermectin on time to resolution of symptoms among adults with mild COVID-19: a randomized clinical trial. *JAMA*. 2021;325(14):1426-1435. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33662102.

28. Chowdhury ATMM, Shahbaz M, Karim MR, et al. A comparative study on ivermectin-doxycycline and hydroxychloroquine-azithromycin therapy on COVID-19 patients. *EJMO*. 2021;5(1):63-70. Available at: https://ejmo.org/pdf/A%20Comparative%20Study%20on%20IvermectinDoxycycline%20and%20HydroxychloroquineAzithromycin%20Therapy%20on%20COVID19%20Patients-16263.pdf.

29. Ravikirti, Roy R, Pattadar C, et al. Evaluation of ivermectin as a potential treatment for mild to moderate COVID-19: a double-blind randomized placebo controlled trial in Eastern India. *J Pharm Pharm Sci*. 2021;24:343-350. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34265236.

30. Mohan A, Tiwari P, Suri TM, et al. Single-dose oral ivermectin in mild and moderate COVID-19 (RIVET-COV): a single-centre randomized, placebo-controlled trial. *J Infect Chemother*. 2021;27(12):1743-1749. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34483029.

31. Galan LEB, Santos NMD, Asato MS, et al. Phase 2 randomized study on chloroquine, hydroxychloroquine or ivermectin in hospitalized patients with severe manifestations of SARS-CoV-2 infection. *Pathog Glob Health*. 2021;115(4):235-242. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33682640.

32. Niaee MS, Namdar P, Allami A, et al. Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: a randomized multi-center clinical trial. *Asian Pac J Trop Med*. 2021;14:266-273. Available at: https://www.apjtm.org/article.asp?issn=1995-7645;year=2021;volume=14;issue=6;spage=266;epage=273;aulast=Shakhsi.

33. Lawrence JM, Meyerowitz-Katz G, Heathers JAJ, Brown NJL, Sheldrick KA. The lesson of ivermectin: meta-analyses based on summary data alone are inherently unreliable. *Nat Med*. 2021;27(11):1853-1854. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34552263.

Lopinavir/Ritonavir and Other HIV Protease Inhibitors

Last Updated: February 11, 2021

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

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

Recommendations

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

Rationale

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

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

Adverse Events

The adverse events for lopinavir/ritonavir include:

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

Drug-Drug Interactions

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

Summary of Clinical Data for COVID-19

- The plasma drug concentrations achieved using typical doses of lopinavir/ritonavir are far below the levels that may be needed to inhibit SARS-CoV-2 replication.[3]
- Lopinavir/ritonavir did not demonstrate a clinical benefit in hospitalized patients with COVID-19 during a large randomized trial in the United Kingdom.[4]

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

Clinical Data for COVID-19

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

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

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

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

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

Patient Characteristics

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

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

Results

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

Limitations

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

Interpretation

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

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

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

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

Patient Characteristics

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

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

Results

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

Limitations

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

Interpretation

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

Lopinavir/Ritonavir Pharmacokinetics in Patients With COVID-19

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

Results

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

Limitations

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

Interpretation

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

Other Reviewed Studies

The Panel has reviewed other clinical studies that evaluated the use of protease inhibitors for the treatment of COVID-19.[6,8,9] These studies have limitations that make them less definitive and

informative than larger randomized clinical trials. The Panel's summaries and interpretations of some of these studies are available in the archived versions of the Guidelines.

References

1. Zumla A, Chan JF, Azhar EI, Hui DS, Yuen KY. Coronaviruses - drug discovery and therapeutic options. *Nat Rev Drug Discov*. 2016;15(5):327-347. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26868298.
2. Marzolini C, Stader F, Stoeckle M, et al. Effect of systemic inflammatory response to SARS-CoV-2 on lopinavir and hydroxychloroquine plasma concentrations. *Antimicrob Agents Chemother*. 2020;64(9). Available at: https://www.ncbi.nlm.nih.gov/pubmed/32641296.
3. Schoergenhofer C, Jilma B, Stimpfl T, Karolyi M, Zoufaly A. Pharmacokinetics of lopinavir and ritonavir in patients hospitalized with coronavirus disease 2019 (COVID-19). *Ann Intern Med*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32422065.
4. Group RC. Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33031764.
5. WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed antiviral drugs for COVID-19—interim WHO Solidarity Trial results. *N Engl J Med*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33264556.
6. Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19. *N Engl J Med.* 2020;382(19):1787-1799. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32187464.
7. Chen J, Xia L, Liu L, et al. Antiviral activity and safety of darunavir/cobicistat for the treatment of COVID-19. *Open Forum Infect Dis*. 2020;7(7):ofaa241. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32671131.
8. Hung IF, Lung KC, Tso EY, et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, Phase 2 trial. *Lancet*. 2020;395(10238):1695-1704. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32401715.
9. Li Y, Xie Z, Lin W, et al. Efficacy and safety of lopinavir/ritonavir or arbidol in adult patients with mild/moderate COVID-19: an exploratory randomized controlled trial. *Med*. 2020:[In Press]. Available at: https://www.sciencedirect.com/science/article/pii/S2666634020300015.

Nitazoxanide

Last Updated: July 8, 2021

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

Recommendation

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

Rationale

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

Please see Table 2e for more information.

Monitoring, Adverse Effects, and Drug-Drug Interactions

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

Considerations in Pregnancy

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

Considerations in Children

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

Clinical Trials

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

References

1. Jasenosky LD, Cadena C, Mire CE, et al. The FDA-approved oral drug nitazoxanide amplifies host antiviral responses and inhibits ebola virus. *iScience*. 2019;19:1279-1290. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31402258.
2. Rossignol JF. Nitazoxanide: a first-in-class broad-spectrum antiviral agent. *Antiviral Res*. 2014;110:94-103. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25108173.
3. Cao J, Forrest JC,Zhang X. A screen of the NIH Clinical Collection small molecule library identifies potential anti-coronavirus drugs. *Antiviral Res*. 2015;114:1-10. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25451075.
4. Haffizulla J, Hartman A, Hoppers M, et al. Effect of nitazoxanide in adults and adolescents with acute uncomplicated influenza: a double-blind, randomised, placebo-controlled, phase 2b/3 trial. *Lancet Infect Dis*. 2014;14(7):609-618. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24852376.
5. Rocco PRM, Silvia PL, Cruz FF, et al. Early use of nitazoxanide in mild COVID-19 disease: randomised, placebo-controlled trial. *Eur Respir J*. 2021;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33361100.
6. Rossignol J, Bardin MC, Oaks JB,et al. Early treatment with nitazoxanide prevents worsening of mild and moderate COVID-19 and subsequent hospitalization. *medRxiv*. 2021;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.04.19.21255441v1.
7. Blum VF, Cimerman S, Hunter JR,et al. Nitazoxanide in vitro efficacy against SARS CoV-2 and in vivo superiority to placebo to treat moderate COVID-19—a Phase 2 randomized double-blind clinical trial. *Preprints with the Lancet*. 2021. Available at: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3763773.
8. Silva M, Espejo A, Pereyra ML, et al. Efficacy of nitazoxanide in reducing the viral load in COVID-19 patients: randomized, placebo-controlled, single-blinded, parallel-group, pilot study. *medRxiv*. 2021;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.03.03.21252509v1.full.pdf.
9. Nitazoxanide (Alinia) [package insert]. Lupin Pharma. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021497s001,021498s004lbl.pdf.

Table 2e. Nitazoxanide: Selected Clinical Data

Last Updated: July 8, 2021

The information in this table may include data from preprints or articles that have not been peer reviewed. This section will be updated as new information becomes available. Please see ClinicalTrials.gov for more information on clinical trials that are evaluating NTZ for the treatment of COVID-19. The clinical trials described in this table do not represent all the trials that the Panel reviewed while developing recommendations for NTZ.[1,2]

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

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

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

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

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

References

1. Blum VF, Cimerman S, Hunter JR, et al. Nitazoxanide superiority to placebo to treat moderate COVID-19–a pilot prove of concept randomized double-blind clinical trial. *EClinicalMedicine*. 2021. Available at: https://pubmed.ncbi.nlm.nih.gov/34222847/.
2. Silva M, Espejo A, Pereyra ML, et al. Efficacy of nitazoxanide in reducing the viral load in COVID-19 patients. Randomized, placebo-controlled, single-blinded, parallel group, pilot study. *medRxiv*. 2021;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.03.03.21252509v1.
3. Rocco PRM, Silva PL, Cruz FF, et al. Early use of nitazoxanide in mild COVID-19 disease: randomised, placebo-controlled trial. *Eur Respir J*. 2021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33361100.
4. Rossignol J, Bardin MC, Oaks JB, et al. Early treatment with nitazoxanide prevents worsening of mild and moderate COVID-19 and subsequent hospitalization. *medRxiv*. 2021;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.04.19.21255441v1.

Table 2f. Characteristics of Antiviral Agents

Last Updated: February 24, 2022

- RDV is the only antiviral drug that is approved by the FDA for the treatment of COVID-19.
- RTV-boosted nirmatrelvir, MOV, and certain anti-SARS-CoV-2 mAbs have received EUAs from the FDA for the treatment of COVID-19.
- Other medications that are currently being evaluated in clinical trials for the treatment of COVID-19 are also included in this table. **The inclusion of these drugs does not imply that the Panel recommends their use.**
- This table focuses on small-molecule antiviral drugs. For more information regarding anti-SARS-CoV-2 mAbs, please see Table 3c.
- Information on CQ, HCQ, and LPV/RTV are available in archived versions of the Guidelines. The Panel **recommends against** using these agents to treat COVID-19.
- For many of these antiviral drugs, there are limited or no data on dose modifications for patients with organ failure or those who require extracorporeal devices. Please refer to product labels, when available.
- There are currently limited data to determine whether certain medications can be safely coadministered with some therapies for the treatment of COVID-19. When using concomitant medications with similar toxicity profiles, consider performing additional safety monitoring.
- For drug interaction information, please refer to product labels, EUA fact sheets, and the Liverpool COVID-19 Drug Interactions website.
- For the Panel's recommendations on using the drugs listed in this table, please refer to the individual drug sections, Therapeutic Management of Nonhospitalized Adults With COVID-19, Therapeutic Management of Hospitalized Adults With COVID-19, or Antiviral Therapy Summary Recommendations.

Dosing Regimens *The doses listed here are for approved indications or from reported experiences or clinical trials.*	**Adverse Events**	**Monitoring Parameters**	**Drug-Drug Interaction Potential**	**Comments and Links to Clinical Trials**
Ritonavir-Boosted Nirmatrelvir (Paxlovid) *Authorized under FDA EUA for the treatment of mild to moderate COVID-19 in high-risk individuals aged ≥12 years and weighing ≥40 kg.*				
EUA Dose for COVID-19[1] *Dosing Based on eGFR:* • ≥60 mL/min: Nirmatrelvir 300 mg (two, 150-mg tablets) with RTV 100 mg (one, 100-mg tablet) twice daily for 5 days • ≥30 to 60 mL/min: Nirmatrelvir 150 mg (one, 150-mg tablet) with RTV 100 mg (one, 100-mg tablet) twice daily for 5 days • <30 mL/min: Not recommended	• Dysgeusia • Diarrhea • HTN • Myalgia	• Monitor for potential AEs due to drug-drug interactions with concomitant medication(s). • Use with caution in patients with pre-existing liver diseases, liver enzyme abnormalities, or hepatitis.	• RTV-boosted nirmatrelvir has significant and complex drug-drug interactions. Before prescribing RTV-boosted nirmatrelvir, **carefully review concomitant medications**, including OTC medicines, herbal supplements, and recreational drugs. See Ritonavir-Boosted Nirmatrelvir (Paxlovid) for more information.	• Both nirmatrelvir and RTV tablets can be taken with or without food.

Dosing Regimens *The doses listed here are for approved indications or from reported experiences or clinical trials.*	**Adverse Events**	**Monitoring Parameters**	**Drug-Drug Interaction Potential**	**Comments and Links to Clinical Trials**
Ritonavir-Boosted Nirmatrelvir (Paxlovid), continued				
Dosing for Patients with Severe Hepatic Impairment (Child-Pugh Class C): • Not recommended			• Consult the EUA fact sheet for Paxlovid, the Liverpool COVID-19 Drug Interactions website, and Table A in Ritonavir-Boosted Nirmatrelvir (Paxlovid) to identify and manage drug-drug interactions.	
Remdesivir *Approved by the FDA for the treatment of COVID-19 in individuals aged ≥12 years and weighing ≥40 kg.*				

Adults and Children (Aged ≥12 Years and Weighing ≥40 kg):
• RDV 200 mg IV on Day 1, then RDV 100 mg IV once daily from Day 2
Dose Recommended in FDA EUA For Children Weighing 3.5 kg to <40 kg:
• RDV 5 mg/kg IV on Day 1, then RDV 2.5 mg/kg IV once daily from Day 2
• Total Treatment Duration:
  • Nonhospitalized patients: 3 days
  • Hospitalized patients: 5 days or until hospital discharge
	• Nausea
	• ALT and AST elevations
	• Hypersensitivity
	• Increases in prothrombin time
	• Drug vehicle is SBECD, which has been associated with renal and liver toxicity. SBECD accumulation may occur in patients with moderate or severe renal impairment.
	• Each 100 mg vial of RDV lyophilized powder contains 3 g of SBECD, and each 100 mg/20 mL vial of RDV solution contains 6 g of SBECD.
	• Clinicians may consider preferentially using the lyophilized powder formulation (which contains less SBECD) in patients with renal impairment.
		• Monitor patients for infusion reactions during the infusion and observe them for ≥1 hour after the infusion as clinically appropriate.
		• Renal function, hepatic function and prothrombin time as clinically indicated
		• FDA does not recommend using RDV when eGFR is <30 mL/min. See the Remdesivir section for information on using RDV in people with renal insufficiency.
			• Clinical drug-drug interaction studies of RDV have not been conducted.
			• In vitro, RDV is a minor substrate of CYP3A4, and a substrate of OATP1B1, and P-gp and an inhibitor of CYP3A4, OATP1B1, OATP1B3, and MATE1.[2]
				• RDV should be administered in settings in which health care providers have immediate access to medications to treat a severe infusion-related reactions or HSR, such as anaphylaxis, and the ability to activate the emergency medical system.
				• A list of clinical trials is available: Remdesivir

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

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

Dosing Regimens *The doses listed here are for approved indications or from reported experiences or clinical trials.*	**Adverse Events**	**Monitoring Parameters**	**Drug-Drug Interaction Potential**	**Comments and Links to Clinical Trials**
Interferon Lambda *Not approved by the FDA and not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*				
PEG-IFN Lambda-1a *Dose for COVID-19 in Clinical Trials:* • Single dose of PEG-IFN lambda-1a 180 µg SUBQ	• Liver function abnormalities • Injection site reactions	• CBC with differential • Liver enzymes • Monitor for potential AEs.	• Low potential for drug-drug interactions • **Use with caution** with other hepatotoxic agents.	• A list of clinical trials is available: Interferon Lambda **Availability:** • PEG-IFN lambda-1a is not approved by the FDA for use in the United States.
Ivermectin *Not approved by the FDA and not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*				
Dose for COVID-19 in Clinical Trials: • IVM 0.2–0.6 mg/kg PO given as a single dose or as a once-daily dose for up to 5 days	• Dizziness • Pruritis • GI effects (e.g., nausea, diarrhea) • Neurological AEs have been reported when IVM has been used to treat parasitic diseases, but it is not clear whether these AEs were caused by IVM or the underlying conditions.	• Monitor for potential AEs.	• Minor CYP3A4 substrate • P-gp substrate	• Generally given on an empty stomach with water; however, administering IVM with food increases its bioavailability.[4] • A list of clinical trials is available: Ivermectin
Nitazoxanide *Not approved by the FDA and not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*				
For Adults: • Doses studied for COVID-19 range from NTZ 500 mg PO 3 times daily to 4 times daily. • Higher doses are being studied. • Doses used for antiprotozoal indications range from NTZ 500 mg–1 g PO twice daily.	• Abdominal pain • Diarrhea • Headache • Nausea • Vomiting • Urine discoloration • Ocular discoloration (rare)	• Monitor for potential AEs.	• Drug-drug interactions may occur if NTZ is administered concurrently with other highly plasma protein-bound drugs due to competition for binding sites.[5] • If NTZ is coadministered with other highly protein-bound drugs with narrow therapeutic indices, monitor the patient for AEs.	• NTZ should be taken with food. • The oral suspension is not bioequivalent to the tablet formulation. • A list of clinical trials is available: Nitazoxanide

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

References

1. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for Paxlovid. 2021. Available at: https://www.fda.gov/media/155050/download.
2. Remdesivir (Veklury) [package insert]. Food and Drug Administration. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/214787Orig1s000lbl.pdf.
3. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for molnupiravir. 2021. Available at: https://www.fda.gov/media/155054/download.
4. Ivermectin (Stromectol) [package insert]. Food and Drug Administration. 2009. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/050742s024s025lbl.pdf.
5. Nitazoxanide (Alinia) [package insert]. Food and Drug Administration. 2016. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021497s001,021498s004lbl.pdf.

Anti-SARS-CoV-2 Antibody Products

Last Updated: February 1, 2022

Summary Recommendations

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

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using a single intravenous infusion of **sotrovimab 500 mg**, administered as soon as possible and within 10 days of symptom onset, to treat nonhospitalized patients (aged ≥12 years and weighing ≥40 kg) with mild to moderate COVID-19 who are at high risk of clinical progression, as defined by criteria in the Food and Drug Administration (FDA) Emergency Use Authorization (EUA) for the product **(AIIa)**.
- Because the B.1.1.529 (Omicron) variant of concern (VOC) has become the dominant variant in the United States and real-time testing to identify rare, non-Omicron variants is not routinely available, the Panel **recommends against** using **bamlanivimab plus etesevimab** or **casirivimab plus imdevimab (AIII)**.
- The strength of the evidence for using anti-SARS-CoV-2 monoclonal antibodies (mAbs) varies depending on the medical conditions and other factors that place patients at risk for progression to severe COVID-19 and/or hospitalization (see Anti-SARS-CoV-2 Monoclonal Antibodies). The ratings for the Panel's recommendations for using anti-SARS-CoV-2 mAbs as treatment are based on the FDA EUA criteria for:
  - High-risk conditions represented in clinical trials **(AIIa)**;
  - Immunocompromising conditions or receipt of immunosuppressive therapy **(AIII)**; *and*
  - Other medical conditions and factors with limited representation in clinical trials **(BIII)**.
- When logistical or supply constraints make it impossible to offer available anti-SARS-CoV-2 mAbs or antiviral therapy to all eligible nonhospitalized patients, see Therapeutic Management of Nonhospitalized Adults With COVID-19 for further guidance.
- Treatment with anti-SARS-CoV-2 mAbs should be started as soon as possible after SARS-CoV-2 infection is confirmed by an antigen test or a nucleic acid amplification test (NAAT) and within 10 days of symptom onset.
- Treatment with anti-SARS-CoV-2 mAbs should be considered for patients with mild to moderate COVID-19 who are hospitalized for a reason other than COVID-19 if they otherwise meet the EUA criteria for outpatient treatment.
- Anti-SARS-CoV-2 mAbs are not currently authorized for use in patients who are hospitalized with severe COVID-19; however, they may be available through expanded access programs for patients who either have not developed an antibody response or are not expected to mount an effective immune response to SARS-CoV-2 infection.

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

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

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

- The Panel recommends using **tixagevimab plus cilgavimab (Evusheld)** administered as intramuscular injections as SARS-CoV-2 pre-exposure prophylaxis (PrEP) for adults and adolescents (aged ≥12 years and weighing ≥40 kg) who do not have SARS-CoV-2 infection, who have not been recently exposed to an individual with SARS-CoV-2 infection, **AND** who:
  - Are moderately to severely immunocompromised and may have an inadequate immune response to COVID-19 vaccination **(BIIa)**; *or*
  - Are not able to be fully vaccinated with any available COVID-19 vaccines due to a documented history of severe adverse reaction to a COVID-19 vaccine or any of its components **(AIIa)**.

Tixagevimab plus cilgavimab is not a substitute for COVID-19 vaccination and should not be used in unvaccinated individuals for whom COVID-19 vaccination is recommended and who are anticipated to have an adequate response.

If supplies of tixagevimab plus cilgavimab are limited, priority for use as PrEP should be given to those who are at the highest risk for severe COVID-19 (see Prevention of SARS-CoV-2 Infection).

Summary Recommendations, continued

COVID-19 Convalescent Plasma
• The Panel **recommends against** the use of **COVID-19 convalescent plasma** for the treatment of COVID-19 in hospitalized patients without impaired humoral immunity **(AI)**.
• There is insufficient evidence for the Panel to recommend either for or against the use of COVID-19 convalescent plasma for the treatment of COVID-19 in:
  • Nonhospitalized patients without impaired humoral immunity; *and*
  • Hospitalized or nonhospitalized patients with impaired humoral immunity.
Anti-SARS-CoV-2 Specific Immunoglobulins
• There is insufficient evidence for the Panel to recommend either for or against the use of anti-SARS-CoV-2 specific immunoglobulins for the treatment of COVID-19.

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

Anti-SARS-CoV-2 Monoclonal Antibodies

Last Updated: February 1, 2022

The SARS-CoV-2 genome encodes 4 major structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N), as well as nonstructural and accessory proteins. The spike protein is further divided into 2 subunits, S1 and S2, that mediate host cell attachment and invasion. Through its receptor-binding domain (RBD), S1 attaches to angiotensin-converting enzyme 2 (ACE2) on the host cell; this initiates a conformational change in S2 that results in virus-host cell membrane fusion and viral entry.[1] Anti-SARS-CoV-2 monoclonal antibodies (mAbs) that target the spike protein have been shown to have clinical benefit in treating SARS-CoV-2 infection (as discussed below). Some anti-SARS-CoV-2 mAbs have been found to be effective as post-exposure prophylaxis (PEP) after a potential exposure to SARS-CoV-2 in a household setting[2] and during SARS-CoV-2 outbreaks in skilled nursing and assisted living facilities.[3] Other anti-SARS-CoV-2 mAbs have been shown to reduce the risk of infection when used as pre-exposure prophylaxis (PrEP).[4]

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

Four anti-SARS-CoV-2 mAb products have received Emergency Use Authorizations (EUAs) from the Food and Drug Administration (FDA). Bamlanivimab plus etesevimab, casirivimab plus imdevimab (REGEN-COV), and sotrovimab received EUAs for the treatment of mild to moderate COVID-19 in nonhospitalized patients with laboratory-confirmed SARS-CoV-2 infection who are at high risk for progressing to severe disease and/or hospitalization. However, the distribution of bamlanivimab plus etesevimab and casirivimab plus imdevimab has been paused because the products have reduced activities against the B.1.1.529 (Omicron) variant of concern (VOC). Sotrovimab is expected to retain efficacy against the Omicron variant.[5] The FDA has issued an EUA for tixagevimab plus cilgavimab (Evusheld), a long-acting anti-SARS-CoV-2 mAb combination. The EUA allows this combination to be used as SARS-CoV-2 PrEP for individuals who do not have SARS-CoV-2 infection, who have not been recently exposed to an individual with SARS-CoV-2 infection, **AND** who are at risk for an inadequate immune response to COVID-19 vaccination **OR** have a documented history of severe adverse reaction to an available COVID-19 vaccine or any of its components (see Prevention of SARS-CoV-2 Infection for more information). The issuance of an EUA does not constitute FDA approval.

These authorized anti-SARS-CoV-2 mAb products are listed alphabetically as follows:

- *Bamlanivimab plus etesevimab:* These are neutralizing mAbs that bind to different, but overlapping, epitopes in the spike protein RBD of SARS-CoV-2.
  - The broad distribution of bamlanivimab plus etesevimab has been paused in the United States because the Omicron variant has markedly reduced in vitro susceptibility to bamlanivimab and etesevimab, and, therefore, this regimen is not expected to provide clinical benefit for patients with Omicron infection.[6]
- *Casirivimab plus imdevimab:* These are recombinant human mAbs that bind to nonoverlapping epitopes of the spike protein RBD of SARS-CoV-2.
  - The broad distribution of casirivimab plus imdevimab has been paused in the United States because the Omicron variant has markedly reduced in vitro susceptibility to casirivimab and imdevimab, and, therefore, this regimen is not expected to provide clinical benefit for patients with Omicron infection.[7]
- *Sotrovimab:* This mAb was originally identified in 2003 from a survivor of SARS-CoV infection.

It targets an epitope in the RBD of the spike protein that is conserved between SARS-CoV and SARS-CoV-2. Sotrovimab retains in vitro activity against the Omicron variant.[8]

- *Tixagevimab plus cilgavimab:* These are recombinant human anti-SARS-CoV-2 mAbs that bind to nonoverlapping epitopes of the spike protein RBD of SARS-CoV-2. Although available in vitro data suggest that the Omicron variant remains susceptible to this combination, more data are needed to fully assess the activity of this regimen when the Omicron variant is circulating at high frequency.[4,9,10]

The FDA has issued an EUA for tixagevimab plus cilgavimab that allows the combination to be used as SARS-CoV-2 PrEP. Before the pause in distribution of bamlanivimab plus etesevimab and casirivimab plus imdevimab, the FDA had expanded the product EUAs to allow the regimens to be used as PEP for certain individuals who are at high risk of acquiring SARS-CoV-2 infection and, if infected, are at high risk of progressing to serious illness. For more information, see the FDA EUA fact sheets for bamlanivimab plus etesevimab and casirivimab plus imdevimab and Prevention of SARS-CoV-2 Infection.

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

The recommendations and discussion below pertain only to the use of the authorized anti-SARS-CoV-2 mAb products for the treatment of COVID-19. For recommendations and discussion regarding the use of anti-SARS-CoV-2 mAb products as PEP or PrEP, see Prevention of SARS-CoV-2 Infection.

The Omicron VOC has become the dominant SARS-CoV-2 variant in the United States.[11] This variant, which includes numerous mutations in the spike protein, has markedly reduced in vitro susceptibility to several anti-SARS-CoV-2 mAbs, especially bamlanivimab plus etesevimab and casirivimab plus imdevimab. Sotrovimab retains in vitro activity against the Omicron variant.

Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using **sotrovimab 500 mg** as a single intravenous (IV) infusion, administered as soon as possible and within 10 days of symptom onset, to treat nonhospitalized patients (aged ≥12 years and weighing ≥40 kg) with mild to moderate COVID-19 who are at high risk of clinical progression **(AIIa)** (see the EUA criteria for use of the product and the related discussion below).
  - Because the Omicron VOC has become the dominant variant in the United States and real-time testing to identify currently rare, non-Omicron variants is not routinely available, the Panel **recommends against** using **bamlanivimab plus etesevimab** or **casirivimab plus imdevimab (AIII)**.
- Treatment with anti-SARS-CoV-2 mAbs should be started as soon as possible after SARS-CoV-2 infection is confirmed by an antigen test or a nucleic acid amplification test (NAAT) and within 10 days of symptom onset.
- Treatment with anti-SARS-CoV-2 mAbs should be considered for patients with mild to moderate COVID-19 who are hospitalized for a reason other than COVID-19 if they otherwise meet the EUA criteria for outpatient treatment.
- Anti-SARS-CoV-2 mAbs are not currently authorized for use in patients who are hospitalized with severe COVID-19; however, the products may be available through expanded access programs for patients who either have not developed an antibody response to SARS-CoV-2 infection or are not expected to mount an effective immune response to infection.
- When logistical or supply constraints make it impossible to offer available therapeutics to all

eligible nonhospitalized patients, see Therapeutic Management of Nonhospitalized Adults With COVID-19 for further guidance.

- There are no data on the combined use of antiviral agents and anti-SARS-CoV-2 mAbs for the treatment of nonhospitalized patients with COVID-19. Clinical trials are needed to determine whether this combination therapy has a role in the treatment of COVID-19.
- Severely immunocompromised patients may have prolonged SARS-CoV-2 replication leading to more rapid viral evolution. There is a theoretic concern that using a single anti-SARS-CoV-2 mAb in these patients may result in emergence of resistant virus. Additional studies are needed to assess this risk. The role of sotrovimab plus antiviral therapy in treating COVID-19 is not yet known.

Rationale

In randomized placebo-controlled trials in nonhospitalized patients who had mild to moderate COVID-19 symptoms and certain risk factors for disease progression, the use of anti-SARS-CoV-2 mAb products reduced the risk of hospitalization and death (see Table 3a).[8,12,13] These studies were conducted before the widespread circulation of the Delta and Omicron VOCs. The potential impact of these variants and their susceptibility to different FDA-authorized anti-SARS-CoV-2 mAbs are discussed below.

Sotrovimab

Sotrovimab retains in vitro activity against the Omicron variant and is expected to provide clinical benefit in patients with Omicron infection.[8] The data that support the EUA for sotrovimab are from the Phase 3 COMET-ICE trial, which included outpatients with mild to moderate COVID-19 who were at high risk for progression to severe disease and/or hospitalization. A total of 583 participants were randomized within 5 days of symptom onset to receive sotrovimab 500 mg IV (n = 291) or placebo (n = 292). The primary endpoint was the proportion of participants who were hospitalized for ≥24 hours or who died from any cause by Day 29. Endpoint events occurred in 3 of 291 participants (1%) in the sotrovimab arm and 21 of 292 participants (7%) in the placebo arm ($P = 0.002$), resulting in a 6% absolute reduction and an 85% relative reduction in hospitalizations or death associated with sotrovimab.[8,14]

Bamlanivimab Plus Etesevimab

The broad distribution of bamlanivimab plus etesevimab has been paused in the United States because the Omicron variant has markedly reduced in vitro susceptibility to this mAb regimen.[6] Prior to the spread of the Omicron variant, the Phase 3 BLAZE-1 trial had demonstrated a clinical benefit of bamlanivimab plus etesevimab in people with mild to moderate COVID-19 who are at high risk for progression to severe disease and/or hospitalization (see Table 3a).[15]

Casirivimab Plus Imdevimab

The broad distribution of casirivimab plus imdevimab has been paused in the United States because the Omicron variant has markedly reduced in vitro susceptibility to this mAb regimen.[7] Prior to the spread of the Omicron variant, the FDA had authorized the use of casirivimab 600 mg plus imdevimab 600 mg administered as a single IV infusion for the treatment of people with mild to moderate COVID-19 who are at high risk for progression to severe disease and/or hospitalization.[8] The FDA also authorized subcutaneous (SQ) injection of the regimen if an IV infusion is not feasible or would delay treatment. SQ administration of casirivimab plus imdevimab requires 4 injections (2.5 mL per injection) at 4 different sites (see the FDA EUA for details).

The recommendation for using the lower dose of casirivimab 600 mg plus imdevimab 600 mg IV is based on data from a Phase 3, double-blind randomized placebo-controlled trial in outpatients with mild to moderate COVID-19. This trial evaluated different doses of casirivimab plus imdevimab administered

as a single IV infusion. The modified full analysis set included participants aged ≥18 years who had a positive SARS-CoV-2 polymerase chain reaction result at randomization and who had ≥1 risk factors for progression to severe COVID-19. The results demonstrated a 2.2% absolute reduction and a 70% relative reduction in hospitalization or death with receipt of casirivimab 600 mg plus imdevimab 600 mg. The results for the higher dose of casirivimab plus imdevimab are comparable: a 3.3% absolute reduction and a 71% relative reduction in hospitalization or death among the patients who received casirivimab 1,200 mg plus imdevimab 1,200 mg.[16] See Table 3a for additional details from the trial.

The recommendation for administering casirivimab plus imdevimab by SQ injections is based on safety data from the Phase 1 R10933-10987-HV-2093 study (ClinicalTrials.gov Identifier NCT04519437). This double-blind randomized placebo-controlled trial compared casirivimab plus imdevimab administered by SQ injection to placebo in healthy volunteers who did not have SARS-CoV-2 infection. Injection site reactions were observed in 12% of the 729 casirivimab plus imdevimab recipients and in 4% of the 240 placebo recipients. According to the FDA EUA for casirivimab plus imdevimab, there were similar reductions in viral load in the IV and SQ arms in a different trial that evaluated the anti-SARS-CoV-2 combination in symptomatic participants.[13] However, because the safety and efficacy data for **casirivimab plus imdevimab** administered by SQ injection are limited, this route of administration should only be used when IV infusion is not feasible or would lead to a delay in treatment **(BIII)**.

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

The FDA EUAs for anti-SARS-CoV-2 mAbs include a list of specific conditions that place patients at high risk for clinical progression. On May 14, 2021, the FDA revised the EUAs to broaden these criteria.[12,13] Notable changes included lowering the body mass index (BMI) cutoff from ≥35 to >25 and adding other conditions and factors (e.g., pregnancy, race or ethnicity). Other than being aged ≥12 years, there are no longer any age criteria restricting the use of these products in patients with the following conditions: sickle cell disease, neurodevelopmental disorders, medical-related technological dependence, asthma, cardiovascular disease, hypertension, and chronic lung disease.

When logistical or supply constraints make it impossible to offer available therapeutics to all eligible nonhospitalized patients, see Therapeutic Management of Nonhospitalized Adults With COVID-19 for further guidance.

Recommendations

The strength of the evidence for using anti-SARS-CoV-2 mAbs varies depending on the medical conditions and other factors that place patients at high risk for progression to severe COVID-19 and/or hospitalization. The ratings for the recommendations for the use of anti-SARS-CoV-2 mAbs as treatment are based on the FDA EUA criteria for identifying high-risk individuals. These criteria include the following conditions and other factors.

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

- Aged ≥65 years **(AIIa)**
- Obesity (BMI >30) **(AIIa)**
- Diabetes **(AIIa)**
- Cardiovascular disease (including congenital heart disease) or hypertension **(AIIa)**
- Chronic lung diseases (e.g., chronic obstructive pulmonary disease, moderate-to-severe asthma, interstitial lung disease, cystic fibrosis, pulmonary hypertension) **(AIIa)**

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

- An immunocompromising condition or immunosuppressive treatment **(AIII)**. Many experts strongly recommend therapy for patients with these conditions, despite their limited representation in clinical trials.
- Being overweight (BMI 25–30) as the sole risk factor **(BIII)**
- Chronic kidney disease **(BIII)**
- Pregnancy **(BIII)**
- Sickle cell disease **(BIII)**
- Neurodevelopmental disorders (e.g., cerebral palsy) or other conditions that confer medical complexity (e.g., genetic or metabolic syndromes and severe congenital anomalies) **(BIII)**
- Medical-related technological dependence (e.g., tracheostomy, gastrostomy, or positive pressure ventilation that is not related to COVID-19) **(BIII)**
- Infants aged <1 year. Although **bamlanivimab plus etesevimab** is authorized for use in this high-risk group, the Panel **recommends against** using this mAb regimen **(AIII)** because it has markedly reduced activity against Omicron, the dominant VOC in the United States.

It is important to note that the likelihood of developing severe COVID-19 increases when a person has multiple high-risk conditions or comorbidities.[17-20] Medical conditions or other factors (e.g., race or ethnicity) that are not listed in the mAb EUAs may also be associated with high risk for progression to severe COVID-19. The current EUAs state that the use of anti-SARS-CoV-2 mAbs may be considered for patients with high-risk conditions and factors that are not listed in the EUAs. For additional information on medical conditions and other factors that are associated with increased risk for progression to severe COVID-19, see the CDC webpage People With Certain Medical Conditions. The decision to use anti-SARS-CoV-2 mAbs for a patient should be based on an individualized assessment of risks and benefits.[8]

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

The anti-SARS-CoV-2 mAbs available through FDA EUAs are not authorized for use in the following patients:

- Those hospitalized for COVID-19; *or*
- Those who require oxygen therapy due to COVID-19; *or*
- Those who are on chronic oxygen therapy due to an underlying non-COVID-19-related comorbidity and who require an increase in oxygen flow rate from baseline because of COVID-19.

The FDA EUAs do permit the use of these products in patients who are hospitalized for a diagnosis other than COVID-19, provided they have mild to moderate COVID-19 and are at high risk for progressing to severe disease.[21-23]

Anti-SARS-CoV-2 mAbs have been evaluated in hospitalized patients with severe COVID-19. A substudy of the ACTIV-3/TICO trial randomized patients who were hospitalized for COVID-19 to receive bamlanivimab 7,000 mg or placebo, each in addition to remdesivir. On October 26, 2020, study enrollment was halted after a prespecified interim futility analysis indicated a lack of clinical benefit for bamlanivimab.[24,25]

Prior to the spread of the Omicron variant, there were data that supported the use of anti-SARS-CoV-2 mAbs in hospitalized patients with COVID-19 who are seronegative for the anti-spike protein antibody and/or with evidence of ongoing viral replication. In a subset analysis of the ACTIV-3 trial, 153 of the 314 participants (49%) were negative for the anti-spike endogenous neutralizing antibody. The subhazard ratio (sHR) comparing bamlanivimab to placebo for sustained recovery (i.e., defined as discharge home and remaining at home for ≥14 days through Day 90) was 1.24 among the participants who were seronegative (CI, 0.90–1.70) versus 0.74 among those who were seropositive (CI, 0.54–1.00). Further, the difference for sustained recovery between bamlanivimab and placebo was even greater among the seronegative participants who had high viral loads (sHR 1.89; CI, 1.23–2.91). However, these results are limited due to the trial's early termination for futility and small sample size.[26]

The ACTIV-3/TICO trial also randomized hospitalized patients with COVID-19 to receive sotrovimab 500 mg IV, an anti-SARS-CoV-2 mAb combination of BRII-196 1,000 mg IV plus BRII-198 1,000 mg IV, or placebo, each in addition to remdesivir. On March 1, 2021, study enrollment was halted after a prespecified interim futility analysis indicated a lack of clinical benefit for sotrovimab or BRII-196 plus BRII-198.[27] A subset analysis did not suggest efficacy for sotrovimab in those with or without endogenous antibodies.

In the RECOVERY study, hospitalized patients with COVID-19 were randomized to receive standard of care with casirivimab 4,000 mg plus imdevimab 4,000 mg IV or standard of care alone. There was no difference in 28-day all-cause mortality between the casirivimab plus imdevimab arm and the standard of care arm; 944 of 4,839 patients (20%) in the casirivimab plus imdevimab arm died versus 1,026 of 4,946 patients (21%) in the standard of care arm (rate ratio 0.94; 95% CI, 0.86–1.03; P = 0.17). However, in the subgroup of patients who were seronegative for the anti-spike protein antibody, there was a significant reduction in 28-day all-cause mortality in the casirivimab plus imdevimab arm (396 of 1,633 casirivimab plus imdevimab recipients [24%] died vs. 451 of 1,520 standard of care recipients [30%]; rate ratio 0.80; 95% CI, 0.70–0.91; P = 0.001).[28] Under the current EUA, this higher dose of casirivimab plus imdevimab is not available, and the lower dose is only authorized for use in nonhospitalized patients with COVID-19. In addition, rapid serology testing that can identify seronegative individuals in real time is currently not widely available.

Anti-SARS-CoV-2 mAbs may be available through expanded access programs for the treatment of immunocompromised patients who are hospitalized because of COVID-19. It is not yet known whether these mAb products provide clinical benefits in people with B cell immunodeficiency or other immunodeficiencies.

SARS-CoV-2 Variants and Their Susceptibility to Anti-SARS-CoV-2 Monoclonal Antibodies

In laboratory studies, some SARS-CoV-2 variants that harbor certain mutations have markedly reduced susceptibility to a number of the authorized anti-SARS-CoV-2 mAbs.[29] The clinical relevance of reduced in vitro susceptibility of select variants to anti-SARS-CoV-2 mAbs is under investigation.

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

- *B.1.1.7 (Alpha):* This variant retains in vitro susceptibility to all the anti-SARS-CoV-2 mAbs that are currently available through FDA EUAs.[12,13,30]
- *B.1.351 (Beta):* This variant has markedly reduced in vitro susceptibility to bamlanivimab and etesevimab.[12,30] In vitro studies also suggest that the Beta variant has markedly reduced susceptibility to casirivimab, although the combination of casirivimab and imdevimab appears to retain activity against the variant. Sotrovimab also appears to retain activity against the variant.[8,13]

- *P.1 (Gamma):* This variant has markedly reduced in vitro susceptibility to bamlanivimab and etesevimab.[12,31] The Gamma variant also has reduced susceptibility to casirivimab; however, the combination of casirivimab plus imdevimab appears to retain activity against the variant. Sotrovimab also appears to retain activity against the Gamma variant.[8,13]
- *B.1.617.2, non-AY.1/AY.2 (Delta):* This VOC retains in vitro susceptibility to all the anti-SARS-CoV-2 mAbs that are currently available through FDA EUAs.[12,13]
- *Omicron:* This is the predominant VOC circulating in the United States. This variant, which includes numerous mutations in the spike protein, has markedly reduced in vitro susceptibility to some anti-SARS-CoV-2 mAb products, including bamlanivimab plus etesevimab and casirivimab plus imdevimab.[9] Sotrovimab retains in vitro activity against this variant.[9,10] In vitro studies have reported a moderate reduction in the susceptibility of Omicron to tixagevimab plus cilgavimab, although this mAb regimen is expected to provide clinical benefit for SARS-CoV-2 PrEP.[9,10,32]

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

WHO Label	Pango Lineage	CDC Variant Class	Notable Mutations	BAM Plus ETE		CAS Plus IMD		SOT		TIX Plus CIL	
				In Vitro Susceptibility[a]	Anticipated Clinical Activity	In Vitro Susceptibility[a]	Anticipated Clinical Activity	In Vitro Susceptibility[a]	Anticipated Clinical Activity	In Vitro Susceptibility[a]	Anticipated Clinical Activity
Alpha	B.1.1.7	VBM	N501Y	No change	Active	No change	Active	No change	Active	No change	Active
Beta	B.1.351	VBM	K417N, E484K, N501Y	Marked reduction	Unlikely to be active	No change[b]	Active	No change	Active	No change	Active
Gamma	P.1	VBM	K417T, E484K, N501Y	Marked reduction	Unlikely to be active	No change[b]	Active	No change	Active	No change	Active
Delta	B.1.617.2, non-AY.1/AY.2	VOC	L452R, T478K	No change	Active	No change	Active	No change	Active	No change	Active
Omicron	B.1.1.529	VOC	K417N, N440K, G446S, E484A, Q493R, N501Y	Marked reduction	Unlikely to be active	Marked reduction	Unlikely to be active	No change	Active	Moderate reduction[c]	Active

[a] Based on the fold reduction in susceptibility reported in the FDA EUAs.[4,8,12,13]

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

[c] Despite moderately reduced in vitro susceptibility, TIX plus CIL is expected to retain activity against the Omicron variant.

Key: BAM = bamlanivimab; CAS = casirivimab; CIL = cilgavimab; CDC = Centers for Disease Control and Prevention; ETE = etesevimab; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; IMD = imdevimab; SOT = sotrovimab; TIX = tixagevimab; VBM = variant being monitored; VOC = variant of concern; WHO = World Health Organization

Ongoing population-based genomic surveillance of the types and proportions of circulating SARS-CoV-2 variants, as well as studies on the susceptibility of different variants to available anti-SARS-CoV-2 mAbs, will be important in defining the utility of specific mAbs in the future.

Clinical Trials

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

Monitoring

Sotrovimab should be administered by IV infusion and should **only be administered in health care settings** by qualified health care providers who have immediate access to emergency medical services and medications that treat severe infusion-related reactions.

Patients should be monitored during the IV infusion and for at least 1 hour after the infusion is completed.

Adverse Effects

Hypersensitivity, including anaphylaxis and infusion-related reactions, has been reported in patients who received anti-SARS-CoV-2 mAbs. Rash, diarrhea, nausea, dizziness, and pruritis have also been reported.[8,13,23]

Drug-Drug Interactions

Drug-drug interactions are unlikely between the authorized anti-SARS-CoV-2 mAbs and medications that are renally excreted or that are cytochrome P450 substrates, inhibitors, or inducers (see Table 3c).

Considerations in Pregnancy

The use of anti-SARS-CoV-2 mAbs can be considered for pregnant people with COVID-19, especially those who have additional risk factors for severe disease (see the EUA criteria for the use of these products above).

As immunoglobulin (Ig) G mAbs, the authorized anti-SARS-CoV-2 mAbs would be expected to cross the placenta. There are no pregnancy-specific data on the use of these mAbs; however, other IgG products have been safely used in pregnant people when their use is indicated. Therefore, authorized anti-SARS-CoV-2 mAbs should not be withheld during pregnancy. When possible, pregnant and lactating people should be included in clinical trials that are evaluating the use of anti-SARS-CoV-2 mAbs for the treatment and/or prevention of COVID-19.

Considerations in Children

Please see Special Considerations in Children for therapeutic recommendations for children with COVID-19.

Drug Availability

Bamlanivimab plus etesevimab, casirivimab plus imdevimab, and sotrovimab are available through FDA EUAs. The broad distribution of bamlanivimab plus etesevimab and casirivimab plus imdevimab has been paused in the United States because the Omicron variant has reduced susceptibility to bamlanivimab and etesevimab, and casirivimab and imdevimab.[6,7] Efforts should be made to ensure that communities most affected by COVID-19 have equitable access to these anti-SARS-CoV-2 mAbs.

References

1. Jiang S, Hillyer C, Du L. Neutralizing antibodies against SARS-CoV-2 and other human coronaviruses. *Trends Immunol*. 2020;41(5):355-359. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32249063.

2. O'Brien MP, Forleo-Neto E, Musser BJ, et al. Subcutaneous REGEN-COV antibody combination to prevent COVID-19. *N Engl J Med*. 2021;385(13):1184-1195. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34347950.
3. Cohen MS, Nirula A, Mulligan MJ, et al. Effect of bamlanivimab vs placebo on incidence of COVID-19 among residents and staff of skilled nursing and assisted living facilities: a randomized clinical trial. *JAMA*. 2021;326(1):46-55. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34081073.
4. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for Evusheld (tixagevimab co-packaged with cilgavimab). 2021. Available at: https://www.fda.gov/media/154701/download.
5. National Center for Advancing Translational Sciences. SARS-CoV-2 variants & therapeutics: therapeutic activity explorer. 2022. Available at: https://opendata.ncats.nih.gov/variant/activity/singlemutationvariant. Accessed January 21, 2022.
6. Public Health Emergency. Bamlanivimab/etesevimab. 2022. Available at: https://www.phe.gov/emergency/events/COVID19/investigation-MCM/Bamlanivimab-etesevimab/Pages/default.aspx. Accessed January 24, 2022.
7. Public Health Emergency. REGEN-COV. 2022. Available at: https://www.phe.gov/emergency/events/COVID19/investigation-MCM/cas_imd/Pages/default.aspx. Accessed January 24, 2022.
8. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of sotrovimab. 2021. Available at: https://www.fda.gov/media/149534/download.
9. Planas D, Saunders N, Maes P, et al. Considerable escape of SARS-CoV-2 Omicron to antibody neutralization. *Nature*. 2021;Advance Article Preview. Available at: https://www.nature.com/articles/d41586-021-03827-2.
10. Cameroni E, Bowen JE, Rosen LE, et al. Broadly neutralizing antibodies overcome SARS-CoV-2 Omicron antigenic shift. *Nature*. 2021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35016195.
11. Centers for Disease Control and Prevention. COVID data tracker: variant proportions. 2021. Available at: https://covid.cdc.gov/covid-data-tracker/#variant-proportions. Accessed December 29, 2021.
12. Food and Drug Administration. Fact sheet for health care providers: emergency use authorization (EUA) of bamlanivimab and etesevimab. 2021. Available at: https://www.fda.gov/media/145802/download.
13. Food and Drug Administration. Fact sheet for health care providers: emergency use authorization (EUA) of REGEN-COV®(casirivimab and imdevimab). 2021. Available at: https://www.fda.gov/media/145611/download.
14. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Early treatment for COVID-19 with SARS-CoV-2 neutralizing antibody sotrovimab. *N Engl J Med*. 2021;385(21):1941-1950. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34706189.
15. Dougan M, Azizad M, Mocherla B, et al. A randomized, placebo-controlled clinical trial of bamlanivimab and etesevimab together in high-risk ambulatory patients with COVID-19 and validation of the prognostic value of persistently high viral load. *Clin Infect Dis*. 2021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34718468.
16. Weinreich DM, Sivapalasingam S, Norton T, et al. REGEN-COV antibody combination and outcomes in outpatients with COVID-19. *N Engl J Med*. 2021;385(23):e81. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34587383.
17. Kim L, Garg S, O'Halloran A, et al. Risk factors for intensive care unit admission and in-hospital mortality among hospitalized adults identified through the US coronavirus disease 2019 (COVID-19)-associated hospitalization surveillance network (COVID-NET). *Clin Infect Dis*. 2021;72(9):e206-e214. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32674114.
18. Guan WJ, Liang WH, Zhao Y, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. *Eur Respir J*. 2020;55(5). Available at: https://www.ncbi.nlm.nih.gov/pubmed/32217650.
19. Zhang Y, Luo W, Li Q, et al. Risk factors for death among the first 80,543 COVID-19 cases in China:

relationships between age, underlying disease, case severity, and region. *Clin Infect Dis*. 2021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34043784.

20. Rosenthal N, Cao Z, Gundrum J, Sianis J, Safo S. Risk factors associated with in-hospital mortality in a US national sample of patients with COVID-19. *JAMA Netw Open*. 2020;3(12):e2029058. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33301018.
21. Food and Drug Administration. Frequently asked questions on the emergency use authorization of casirivimab + imdevimab. 2020. Available at: https://www.fda.gov/media/143894/download.
22. Food and Drug Administration. Frequently asked questions on the emergency use authorization of bamlanivimab and etesevimab. 2021. Available at: https://www.fda.gov/media/145808/download.
23. Food and Drug Administration. Frequently asked questions on the emergency use authorization of sotrovimab. 2021. Available at: https://www.fda.gov/media/149535/download.
24. National Institute of Allergy and Infectious Diseases. Statement—NIH-sponsored ACTIV-3 trial closes LY-CoV555 sub-study. 2020. Available at: https://www.niaid.nih.gov/news-events/statement-nih-sponsored-activ-3-trial-closes-ly-cov555-sub-study.
25. ACTIV-TICO LY-CoV555 Study Group, Lundgren JD, Grund B, et al. A neutralizing monoclonal antibody for hospitalized patients with COVID-19. *N Engl J Med*. 2021;384(10):905-914. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33356051.
26. ACTIV-3/TICO Bamlanivimab Study Group. Responses to a neutralizing monoclonal antibody for hospitalized patients with COVID-19 according to baseline antibody and antigen levels: a randomized controlled trial. *Ann Intern Med*. 2021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34928698.
27. ACTIV-3/Therapeutics for Inpatients with COVID-19 Study Group. Efficacy and safety of two neutralising monoclonal antibody therapies, sotrovimab and BRII-196 plus BRII-198, for adults hospitalised with COVID-19 (TICO): a randomised controlled trial. *Lancet Infect Dis*. 2021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34953520.
28. RECOVERY Collaborative Group, Horby PW, Mafham M, et al. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *medRxiv*. 2021;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.06.15.21258542v1.full.
29. Centers for Disease Control and Prevention. SARS-CoV-2 variant classifications and definitions. 2021. Available at: https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-classifications.html. Accessed January 24, 2022.
30. Wang P, Nair MS, Liu L, et al. Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7. *Nature*. 2021;593(7857):130-135. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33684923.
31. Wang P, Casner RG, Nair MS, et al. Increased resistance of SARS-CoV-2 variant P.1 to antibody neutralization. *Cell Host Microbe*. 2021;29(5):747-751 e744. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33887205.
32. VanBlargan L, Errico J, Halfmann P, et al. An infectious SARS-CoV-2 B.1.1.529 Omicron virus escapes neutralization by therapeutic monoclonal antibodies. *Res Sq*. 2021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34981042.

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

Last Updated: December 16, 2021

This table describes only clinical trials that have evaluated anti-SARS-CoV-2 mAbs for the treatment of COVID-19. Please refer to the Prevention of SARS-CoV-2 Infection section for a discussion of clinical trials that have evaluated anti-SARS-CoV-2 mAbs for PEP of SARS-CoV-2 infection.

Methods	Results	Interpretation
BLAZE-1: Double-Blind, Phase 3 RCT of Bamlanivimab 700 mg Plus Etesevimab 1,400 mg in Nonhospitalized Patients With Mild to Moderate COVID-19[1]		

Key Inclusion Criteria:
• Aged ≥12 years
• At high risk for severe COVID-19 or hospitalization
Interventions:
• Within 3 days of a positive SARS-CoV-2 test result, single infusion of:
  • BAM 700 mg plus ETE 1,400 mg (n = 511)
  • Placebo (n = 258)
Primary Endpoint:
• 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% ≥65 years; 53% women
	• 87% White, 27% Hispanic/Latinx, 8% Black/African American
	• Mean duration of symptoms was 4 days.
	• 76% had mild COVID-19 and 24% had moderate COVID-19.
	Primary Outcomes:
	• COVID-19-related hospitalizations or all-cause deaths by Day 29: 4 (0.8%) in BAM plus ETE arm vs. 15 (5.8%) in placebo arm (Δ [95% CI] = -5.0 [-8.0, -2.1]; P <0.001).
	• All-cause deaths by Day 29: 0 in BAM plus ETE arm vs. 4 (1.6%) in placebo arm.
		Interpretation:
		• Compared to placebo, BAM plus ETE was associated with 5% absolute reduction and 87% relative reduction in COVID-19-related hospitalizations or all-cause deaths.

BLAZE-1: Double-Blind, Phase 3 RCT of Bamlanivimab 2,800 mg Plus Etesevimab 2,800 mg in Nonhospitalized Patients With Mild to Moderate COVID-19[2]		

Key Inclusion Criteria:
• Aged ≥12 years
• At high risk for severe COVID-19 or hospitalization
Key Exclusion Criteria:
• SpO_2 ≤93% on room air; *or*
• Respiratory rate ≥30 breaths/min; *or*
• Heart rate ≥125 bpm
Interventions:
• Within 3 days of testing SARS-CoV-2 positive, single infusion of:
  • BAM 2,800 mg plus ETE 2,800 mg (n = 518)
  • Placebo (n = 517)
	Participant Characteristics:
	• Mean age 53.8 years; 31% ≥65 years; 52% women; 48% men
	• 87% White, 29% Hispanic/Latinx, 8% Black/African American
	• Median days from symptom onset to infusion was 4 days.
	• 77% had mild COVID-19.
	Primary Outcomes:
	• COVID-19-related hospitalizations or all-cause deaths by Day 29: 11 (2.1%) in BAM plus ETE arm vs. 36 (7.0%) in placebo arm; relative risk difference: 70% (P < 0.001).
	• All-cause deaths by Day 29: 0 in BAM plus ETE arm vs. 10 (1.9%) in placebo arm.
		Interpretation:
		• Compared to placebo, BAM plus ETE was associated with 4.8% absolute reduction and 70% relative reduction in COVID-19-related hospitalizations or all-cause deaths.

Methods	Results	Interpretation
BLAZE-1: Double-Blind, Phase 3 RCT of Bamlanivimab 2,800 mg Plus Etesevimab 2,800 mg in Nonhospitalized Patients With Mild to Moderate COVID-19[2], continued		
Primary Endpoint: • COVID-19-related hospitalization or death from any cause by Day 29 **Secondary Endpoint:** • SARS-CoV-2 VL >5.27 $\log_{10}$ copies/mL at Day 7	**Secondary Outcome:** • Percentage of patients with SARS-CoV-2 VL >5.27 $\log_{10}$ copies/mL at Day 7: 9.8% in BAM plus ETE arm vs. 29.5% in placebo arm ($P < 0.001$).	
Double-Blind, Phase 3 RCT of Casirivimab Plus Imdevimab in Nonhospitalized Patients With Mild to Moderate COVID-19[3]		

Key Inclusion Criteria:
• Aged ≥18 years
• 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 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 through Day 29
	Participant Characteristics:
	• Median age 50 years; 35% Hispanic/Latinx, 5% Black/African American
	• Median duration of symptoms prior to enrollment was 3 days.
	Primary Outcomes:
	• COVID-19-related hospitalizations or all-cause deaths through Day 29:
	  • 7 (1.0%) in CAS 600 mg plus IMD 600 mg arm vs. 24 (3.2%) in placebo arm ($P = 0.002$).
	  • 18 (1.3%) in CAS 1,200 mg plus IMD 1,200 mg arm vs. 62 (4.6%) in placebo arm ($P < 0.001$).
	All-Cause Deaths:
	• 1 (0.1%) in CAS 600 mg plus IMD 600 mg arm vs. 1 (0.1%) in placebo arm.
	• 1 (< 0.1%) in CAS 1,200 mg plus IMD 1,200 mg arm vs. 3 (0.2%) in placebo arm.
		Interpretation:
		• Compared to placebo, CAS 600 mg plus IMD 600 mg was associated with 2.2% absolute reduction and 70% relative risk reduction in COVID-19-related hospitalizations or all-cause deaths.
		• Compared to placebo, CAS 1,200 mg plus IMD 1,200 mg was associated with 3.3% absolute reduction and 71% relative risk reduction in COVID-19-related hospitalizations or all-cause deaths.

Methods	Results	Interpretation
COMET-ICE: Double-Blind, Phase 3 RCT of Sotrovimab in Nonhospitalized Patients With Mild to Moderate COVID-19, Interim Analysis[4]		
Key Inclusion Criteria: • Aged ≥18 years with ≥1 comorbidity or aged ≥55 years • Laboratory-confirmed COVID-19 • Symptom onset ≤5 days before enrollment **Key Exclusion Criteria:** • Hospitalized or requiring supplemental oxygen • Severely immunocompromised **Interventions:** • SOT 500 mg IV (n = 291) • Placebo (n = 292) **Primary Endpoint:** • Hospitalization or death from any cause by Day 29	**Participant Characteristics:** • Median age 53 years; 22% ≥65 years • 63% Hispanic/Latinx, 7% Black/African American **Primary Outcome:** • Hospitalizations or all-cause deaths by Day 29: 3 (1%) in SOT arm vs. 21 (7%) in placebo arm (P = 0.002).	**Interpretation:** • Compared to placebo, SOT was associated with 6% absolute reduction and 85% relative risk reduction in all-cause hospitalizations or deaths.

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

References

1. Dougan M, Azizad M, Mocherla B, et al. A randomized, placebo-controlled clinical trial of bamlanivimab and etesevimab together in high-risk ambulatory patients with COVID-19 and validation of the prognostic value of persistently high viral load. *Clin Infect Dis*. 2021;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34718468.
2. Dougan M, Nirula A, Azizad M, et al. Bamlanivimab plus etesevimab in mild or moderate COVID-19. *N Engl J Med*. 2021;385(15):1382-1392. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34260849.
3. Weinreich DM, Sivapalasingam S, Norton T, et al. REGEN-COV antibody combination and outcomes in outpatients with COVID-19. *N Engl J Med*. 2021;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34587383.
4. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Early treatment for COVID-19 with SARS-CoV-2 neutralizing antibody sotrovimab. *N Engl J Med*. 2021;385(15):1382-1392. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34706189.

Convalescent Plasma

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Plasma from donors who have recovered from COVID-19 may contain antibodies to SARS-CoV-2 that could help suppress viral replication.[1] In August 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for convalescent plasma for the treatment of hospitalized patients with COVID-19. On February 4, 2021, the FDA revised the convalescent plasma EUA to limit the authorization to high-titer COVID-19 convalescent plasma and only for the treatment of hospitalized patients with COVID-19 early in their disease course or hospitalized patients who have impaired humoral immunity.[2] Use of convalescent plasma should be limited to those products that contain high levels of anti-SARS-CoV-2 antibodies (i.e., high-titer products). Products that are not labeled "high titer" should not be used.

Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of **COVID-19 convalescent plasma** for the treatment of COVID-19 in hospitalized patients without impaired humoral immunity **(AI)**.
- There is insufficient evidence for the Panel to recommend either for or against the use of COVID-19 convalescent plasma for the treatment of COVID-19 in:
  - Nonhospitalized patients without impaired humoral immunity; *and*
  - Nonhospitalized or hospitalized patients with impaired humoral immunity.

Rationale

For Hospitalized Patients Without Impaired Humoral Immunity

Clinical data on the use of convalescent plasma for the treatment of COVID-19, including data from several randomized trials and the U.S. Expanded Access Program (EAP) for Convalescent Plasma, are summarized in Table 3b.

The EUA for convalescent plasma for the treatment of hospitalized patients with COVID-19 was issued on the basis of retrospective, indirect evaluations of efficacy generated from the convalescent plasma EAP, which allowed for its use regardless of titer. Several retrospective analyses of the EAP data indicated that patients who received high-titer plasma had a lower relative risk of death than patients who received low-titer plasma.[3,4] The Panel reviewed the EAP analyses and determined that the data were not sufficient to establish the efficacy or safety of COVID-19 convalescent plasma due to potential confounding, the lack of randomization, and the lack of an untreated control group.

Data from the initial randomized clinical trials evaluating convalescent plasma, which were all underpowered, did not demonstrate the product's efficacy for the treatment of hospitalized patients with COVID-19.[5-12]

Subsequently, results from the 3 largest randomized clinical trials evaluating convalescent plasma in hospitalized patients—RECOVERY,[13] CONCOR-1,[14] and REMAP-CAP[15]—found no evidence of benefit from high-titer convalescent plasma in hospitalized patients with COVID-19. All 3 were open-label trials that were stopped early due to futility.

In the RECOVERY trial, patients were randomized to receive convalescent plasma (n = 5,795) or usual care (n = 5,763). The trial demonstrated no significant difference in the primary endpoint of 28-day

mortality between the convalescent plasma arm and the usual care arm (24% in each arm; risk ratio 1.00; 95% CI, 0.93–1.07). Additionally, there were no differences between the arms in the secondary endpoints of time to hospital discharge and receipt of mechanical ventilation or death.

In the CONCOR-1 trial, patients were randomized to receive convalescent plasma or standard of care. The primary endpoint of intubation or death by Day 30 occurred in 199 of 614 patients (32%) in the convalescent plasma arm and 86 of 307 patients (28%) in the standard of care arm (relative risk 1.16; 95% CI, 0.94–1.43). There were no differences between the arms in secondary endpoints, including time to intubation or death, mortality, or intensive care unit and hospital length of stay. Serious adverse events occurred in 33% of the patients in the convalescent plasma arm and 26% of those in the standard of care arm, including 35 transfusion-related complications reported in the convalescent plasma arm.

The REMAP-CAP trial evaluated convalescent plasma in hospitalized patients. Although noncritically ill patients participated in the study, the reported outcomes are only for those who were critically ill at enrollment (1,084 patients in the convalescent plasma arm and 916 patients in the control arm). There was no difference in the primary endpoint of organ support-free days up to Day 21 between the arms (median of 0 days in the convalescent plasma arm [IQR -1 to 16 days] vs. 3 days in the control arm [IQR -1 to 16 days]). There were also no differences between the arms in secondary endpoints, including in-hospital mortality (401 of 1,075 patients [37.3%] in the convalescent plasma arm died vs. 347 of 904 patients [38.4%] in the control arm). The study showed a potential for harm (90.3% posterior probability) in 126 patients who were randomized to convalescent plasma after >7 days of hospitalization.

Although these trials did not exclude patients with impaired humoral immunity, most of the patients enrolled did not report a history of an immunocompromising condition or receipt of chronic immunosuppressive therapy. Based on the collective results from these studies, the Panel **recommends against** the use of **COVID-19 convalescent plasma** for the treatment of COVID-19 in hospitalized patients who do not have impaired humoral immunity **(AI)**.

For Nonhospitalized Patients Without Impaired Humoral Immunity

Current data are insufficient to establish the safety or efficacy of convalescent plasma in nonhospitalized patients with COVID-19. Convalescent plasma is not authorized for nonhospitalized patients with COVID-19 under the EUA.

Data from a double-blind, placebo-controlled, randomized trial of high-titer convalescent plasma in older, nonhospitalized adults with <72 hours of mild COVID-19 symptoms demonstrated benefit in reduced progression of respiratory disease.[4] However, the trial included relatively few participants (80 participants in each arm).

The C3PO study was a single-blind randomized trial that evaluated high-titer convalescent plasma for the treatment of nonhospitalized patients with ≤7 days of mild or moderate COVID-19 symptoms and at least 1 risk factor for severe COVID-19.[16] Trial participants (n = 511) were randomized to receive convalescent plasma or a placebo transfusion. The trial was halted after a second interim analysis indicated a priori futility criteria were reached. There was no difference in the occurrence of the composite primary endpoint of disease progression (i.e., hospital admission, death without hospitalization, or urgent or emergency care within 15 days after randomization) between the patients in the convalescent plasma arm and the placebo arm (30% vs. 32%; risk difference 1.9%; 95% CI, -6.0 to 9.8). There were no differences between the arms in any secondary endpoints, including the worst severity of illness based on an 8-point ordinal scale and hospital-free days after randomization. Five patients in the convalescent plasma arm and 1 patient in the placebo arm died. Infusion-related reactions,

which occurred more often in the convalescent plasma arm, included 3 serious reactions.

Results from additional, adequately powered, well-designed, and well-conducted randomized clinical trials are needed to provide more specific, evidence-based guidance on the role of COVID-19 convalescent plasma in the treatment of nonhospitalized patients with COVID-19.

The FDA has issued EUAs for several anti-SARS-CoV-2 monoclonal antibody products for the treatment of nonhospitalized patients with mild to moderate COVID-19 who are at high risk of progression to severe disease (see Anti-SARS-CoV-2 Monoclonal Antibodies). The Panel recommends using these products for the population specified in the EUAs.

For Hospitalized or Nonhospitalized Patients With Impaired Humoral Immunity

People who are immunocompromised are more likely to become severely ill from COVID-19, experience prolonged SARS-CoV-2 infection and shedding, and require hospitalization for breakthrough SARS-CoV-2 infection despite COVID-19 vaccination.[17,18] Although some of this vulnerability may be attributed to impaired cellular immune responses, numerous studies indicate that people who are immunosuppressed are at risk of reduced antibody responses to SARS-CoV-2 infection and vaccination.[19-21] An analysis from the RECOVERY trial suggests that SARS-CoV-2 seronegative patients are more likely to benefit from convalescent plasma than seropositive patients.[22] Therefore, convalescent plasma may be effective in SARS-CoV-2 seronegative patients even though no benefit was observed in the overall population of patients enrolled in the RECOVERY trial.

The REMAP-CAP investigators performed a prespecified subgroup analysis of 126 patients with immunodeficiencies who were critically ill.[15] Immunodeficiency was defined as recent chemotherapy or radiation, high-dose or long-term steroid use, or presence of immunocompromising diseases. Although not statistically significant, results of this analysis suggest that, compared to placebo, convalescent plasma offers a potential benefit of improved survival and/or more organ support-free days in this subgroup of immunocompromised patients (OR 1.51; 95% CI, 0.80–2.92).

Severely immunocompromised individuals may experience prolonged SARS-CoV-2 infection with persistent viral replication over several months, as described in the case report of a patient with lymphoma who had received chimeric antigen receptor T cell therapy and who subsequently recovered following repeat transfusions of high-dose convalescent plasma.[23] Data from case reports, case series, and a retrospective case-control study also suggest a potential benefit of convalescent plasma in patients with primary and secondary humoral immunodeficiencies, including patients with hematologic malignancy, common variable immune deficiency, or agammaglobulinemia, and those who have received a solid organ transplant.[24-37]

Although there is physiologic rationale for the value of convalescent plasma in immunocompromised people and some reports suggesting benefit, there are no definitive data to support the use of convalescent plasma in this patient population. Therefore, there is insufficient evidence for the Panel to recommend either for or against the use of COVID-19 convalescent plasma for the treatment of COVID-19 in hospitalized or nonhospitalized patients who have impaired humoral immunity. Adequately powered, well-designed, and well-conducted randomized clinical trials are needed to provide more specific, evidence-based guidance on the role of convalescent plasma in the treatment of patients with COVID-19 who have impaired humoral immunity.

Clinical Data to Date

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

Considerations in Pregnancy

The safety and efficacy of using COVID-19 convalescent plasma during pregnancy have not been evaluated in clinical trials, and published data on its use in pregnant individuals with COVID-19 are limited to case reports.[38] 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.[39,40] If otherwise indicated, pregnancy is not a reason to withhold convalescent plasma.

Considerations in Children

The safety and efficacy of COVID-19 convalescent plasma have not been systematically evaluated in pediatric patients. Published literature on its use in children is limited to case reports and case series, as well as a systematic review of these reports. A few clinical trials of COVID-19 convalescent plasma in children are ongoing. The use of convalescent plasma may be considered on a case-by-case basis for hospitalized children with impaired immunity who meet the EUA criteria for its use. Convalescent plasma is not authorized by the FDA for use in nonhospitalized patients with COVID-19.

Several anti-SARS-CoV-2 monoclonal antibody products have received EUAs for treatment of nonhospitalized patients aged ≥12 years with mild to moderate COVID-19 who are at high risk of progression to severe disease. Use of these products may be considered on a case-by-case basis for children who meet the EUA criteria (see Anti-SARS-CoV-2 Monoclonal Antibodies).

Adverse Effects

Available data suggest that serious adverse reactions following the administration of COVID-19 convalescent plasma are infrequent and consistent with the risks associated with plasma infusions for other indications. These risks include transfusion-transmitted infections (e.g., HIV, hepatitis B, hepatitis C), allergic reactions, anaphylactic reactions, febrile nonhemolytic reactions, transfusion-related acute lung injury, transfusion-associated circulatory overload, and hemolytic reactions. Hypothermia, metabolic complications, and post-transfusion purpura have also been described.[2,41,42]

Additional risks of COVID-19 convalescent plasma transfusion include a theoretical risk of antibody-dependent enhancement of SARS-CoV-2 infection and a theoretical risk of long-term immunosuppression. In the CONCOR-1 trial, higher levels of full transmembrane spike IgG were associated with worse outcomes, suggesting the use of convalescent plasma with nonfunctional anti-SARS-CoV-2 antibodies may be harmful.[14] Subgroup analysis in the REMAP-CAP trial showed potential harm in convalescent plasma transfused >7 days into hospitalization.[15]

When considering convalescent plasma for patients with a history of severe allergic or anaphylactic transfusion reactions, consultation with a transfusion medicine specialist is advised.

Clinical Trials

Randomized clinical trials evaluating convalescent plasma for the treatment of COVID-19 are underway. Please see ClinicalTrials.gov for the latest information.

References

1. Wang X, Guo X, Xin Q, et al. Neutralizing antibodies responses to SARS-CoV-2 in COVID-19 inpatients and convalescent patients. *Clin Infect Dis*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32497196.
2. Food and Drug Administration. EUA of COVID-19 convalescent plasma for the treatment of COVID-19 in hospitalized patients: fact sheet for health care providers. 2020. Available at:

https://www.fda.gov/media/141478/download.

3. Joyner MJ, Carter RE, Senefeld JW, et al. Convalescent plasma antibody levels and the risk of death from COVID-19. *N Engl J Med*. 2021;384(11):1015-1027. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33523609.
4. Libster R, Perez Marc G, Wappner D, et al. Early high-titer plasma therapy to prevent severe COVID-19 in older adults. *N Engl J Med*. 2021;384(7):610-618. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33406353.
5. Simonovich VA, Burgos Pratx LD, Scibona P, et al. A randomized trial of convalescent plasma in COVID-19 severe pneumonia. *N Engl J Med*. 2021;384(7):619-629. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33232588.
6. Agarwal A, Mukherjee A, Kumar G, et al. Convalescent plasma in the management of moderate COVID-19 in adults in India: open label Phase II multicentre randomised controlled trial (PLACID Trial). *BMJ*. 2020;371:m3939. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33093056.
7. Li L, Zhang W, Hu Y, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. *JAMA*. 2020;324(5):460-470. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32492084.
8. Gharbharan A, Jordans CCE, GeurtsvanKessel C, et al. Effects of potent neutralizing antibodies from convalescent plasma in patients hospitalized for severe SARS-CoV-2 infection. *Nat Commun*. 2021;12(1):3189. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34045486.
9. Avendano-Sola C, Ramos-Martinez A, Munez-Rubio E, et al. A multicenter randomized open-label clinical trial for convalescent plasma in patients hospitalized with COVID-19 pneumonia. *J Clin Invest*. 2021;131(20). Available at: https://www.ncbi.nlm.nih.gov/pubmed/34473652.
10. AlQahtani M, Abdulrahman A, Almadani A, et al. Randomized controlled trial of convalescent plasma therapy against standard therapy in patients with severe COVID-19 disease. *Sci Rep*. 2021;11(1):9927. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33976287.
11. Ray Y, Ranjan Paul SR, Bandopadhyay P, et al. Clinical and immunological benefits of convalescent plasma therapy in severe COVID-19: insights from a single center open label randomised control trial. *medRxiv*. 2020;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2020.11.25.20237883v1.
12. O'Donnell MR, Grinsztejn B, Cummings MJ, et al. A randomized double-blind controlled trial of convalescent plasma in adults with severe COVID-19. *J Clin Invest*. 2021;131(13). Available at: https://www.ncbi.nlm.nih.gov/pubmed/33974559.
13. RECOVERY Collaborative Group. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial. *Lancet*. 2021;397(10289):2049-2059. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34000257.
14. Begin P, Callum J, Jamula E, et al. Convalescent plasma for hospitalized patients with COVID-19: an open-label, randomized controlled trial. *Nat Med*. 2021;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34504336.
15. Writing Committee for the Remap-CAP Investigators, Estcourt LJ, Turgeon AF, et al. Effect of convalescent plasma on organ support-free days in critically ill patients with COVID-19: a randomized clinical trial. *JAMA*. 2021;326(17):1690-1702. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34606578.
16. Korley FK, Durkalski-Mauldin V, Yeatts SD, et al. Early convalescent plasma for high-risk outpatients with COVID-19. *N Engl J Med*. 2021;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34407339.
17. Brosh-Nissimov T, Orenbuch-Harroch E, Chowers M, et al. BNT162b2 vaccine breakthrough: clinical characteristics of 152 fully vaccinated hospitalized COVID-19 patients in Israel. *Clin Microbiol Infect*. 2021;27(11):1652-1657. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34245907.
18. Tenforde MW, Patel MM, Ginde AA, et al. Effectiveness of SARS-CoV-2 mRNA vaccines for preventing

COVID-19 hospitalizations in the United States. *Clin Infect Dis*. 2021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34358310.

19. Hallett AM, Greenberg RS, Boyarsky BJ, et al. SARS-CoV-2 messenger RNA vaccine antibody response and reactogenicity in heart and lung transplant recipients. *J Heart Lung Transplant*. 2021;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34456108.
20. Grupper A, Rabinowich L, Schwartz D, et al. Reduced humoral response to mRNA SARS-CoV-2 BNT162b2 vaccine in kidney transplant recipients without prior exposure to the virus. *Am J Transplant*. 2021;21(8):2719-2726. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33866672.
21. Herishanu Y, Avivi I, Aharon A, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. *Blood*. 2021;137(23):3165-3173. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33861303.
22. Hamilton FW, Lee T, Arnold DT, Lilford R, Hemming K. Is convalescent plasma futile in COVID-19? A Bayesian re-analysis of the RECOVERY randomized controlled trial. *Int J Infect Dis*. 2021;109:114-117. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34157385.
23. Nussenblatt V, Roder AE, Das S, et al. Year-long COVID-19 infection reveals within-host evolution of SARS-CoV-2 in a patient with B cell depletion. *J Infect Dis*. 2021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34940844.
24. Ferrari S, Caprioli C, Weber A, Rambaldi A, Lussana F. Convalescent hyperimmune plasma for chemo-immunotherapy induced immunodeficiency in COVID-19 patients with hematological malignancies. *Leuk Lymphoma*. 2021;62(6):1490-1496. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33461387.
25. Hueso T, Pouderoux C, Pere H, et al. Convalescent plasma therapy for B-cell-depleted patients with protracted COVID-19. *Blood*. 2020;136(20):2290-2295. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32959052.
26. Rahman F, Liu STH, Taimur S, et al. Treatment with convalescent plasma in solid organ transplant recipients with COVID-19: Experience at large transplant center in New York City. *Clin Transplant*. 2020;34(12):e14089. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32918761.
27. Mira E, Yarce OA, Ortega C, et al. Rapid recovery of a SARS-CoV-2-infected X-linked agammaglobulinemia patient after infusion of COVID-19 convalescent plasma. *J Allergy Clin Immunol Pract*. 2020;8(8):2793-2795. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32652231.
28. Fung M, Nambiar A, Pandey S, et al. Treatment of immunocompromised COVID-19 patients with convalescent plasma. *Transpl Infect Dis*. 2021;23(2):e13477. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32989856.
29. Quinti I, Lougaris V, Milito C, et al. A possible role for B cells in COVID-19? Lesson from patients with agammaglobulinemia. *J Allergy Clin Immunol*. 2020;146(1):211-213 e214. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32333914.
30. Jin H, Reed JC, Liu STH, et al. Three patients with X-linked agammaglobulinemia hospitalized for COVID-19 improved with convalescent plasma. *J Allergy Clin Immunol Pract*. 2020;8(10):3594-3596 e3593. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32947026.
31. Betrains A, Godinas L, Woei AJF, et al. Convalescent plasma treatment of persistent severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection in patients with lymphoma with impaired humoral immunity and lack of neutralising antibodies. *Br J Haematol*. 2021;192(6):1100-1105. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33314018.
32. Balashov D, Trakhtman P, Livshits A, et al. SARS-CoV-2 convalescent plasma therapy in pediatric patient after hematopoietic stem cell transplantation. *Transfus Apher Sci*. 2021;60(1):102983. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33153902.
33. Thompson MA, Henderson JP, Shah PK, et al. Association of convalescent plasma therapy with survival in patients with hematologic cancers and COVID-19. *JAMA Oncol*. 2021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34137799.

34. Senefeld JW, Klassen SA, Ford SK, et al. Use of convalescent plasma in COVID-19 patients with immunosuppression. *Transfusion*. 2021;61(8):2503-2511. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34036587.

35. Clark E, Guilpain P, Filip IL, et al. Convalescent plasma for persisting COVID-19 following therapeutic lymphocyte depletion: a report of rapid recovery. *Br J Haematol*. 2020;190(3):e154-e156. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32593180.

36. Van Damme KFA, Tavernier S, Van Roy N, et al. Case report: convalescent plasma, a targeted therapy for patients with CVID and severe COVID-19. *Front Immunol*. 2020;11:596761. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33329586.

37. Tremblay D, Seah C, Schneider T, et al. Convalescent plasma for the treatment of severe COVID-19 infection in cancer patients. *Cancer Med*. 2020;9(22):8571-8578. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32945149.

38. Franchini M, Prefumo F, Grisolia G, et al. Convalescent plasma for pregnant women with COVID-19: a systematic literature review. *Viruses*. 2021;13(7). Available at: https://www.ncbi.nlm.nih.gov/pubmed/34206468.

39. Revello MG, Lazzarotto T, Guerra B, et al. A randomized trial of hyperimmune globulin to prevent congenital cytomegalovirus. *N Engl J Med*. 2014;370(14):1316-1326. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24693891.

40. Hughes BL, Clifton RG, Rouse DJ, et al. A trial of hyperimmune globulin to prevent congenital cytomegalovirus infection. *N Engl J Med*. 2021;385(5):436-444. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34320288.

41. Nguyen FT, van den Akker T, Lally K, et al. Transfusion reactions associated with COVID-19 convalescent plasma therapy for SARS-CoV-2. *Transfusion*. 2021;61(1):78-93. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33125158.

42. The RECOVERY Collaborative Group, Horby PW, Estcourt L, et al. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *medRxiv*. 2021;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.03.09.21252736v1.

Table 3b. COVID-19 Convalescent Plasma: Selected Clinical Data

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

Note: The current EUA for COVID-19 CP is limited to the use of high-titer CP. Refer to the revised EUA Letter of Authorization for a list of anti-SARS-CoV-2 antibody tests that can be used to qualify COVID-19 CP as high titer.

Methods	Results	Limitations and Interpretation
REMAP-CAP: Multinational, Open-Label RCT of High-Titer Convalescent Plasma in Hospitalized Patients With Critical COVID-19[1]		
Key Inclusion Criteria: • Admitted to ICU with receipt of respiratory support (HFNC oxygen, NIV, MV, ECMO) and/or vasopressor or inotrope support **Key Exclusion Criteria:** • CP contraindicated • Death imminent **Interventions:** • High-titer CP (550 mL +/- 150 mL) within 48 hours of randomization (n = 1,084) • Usual care (n = 916) **Primary Endpoint:** • Organ support-free days by Day 21 **Key Secondary Endpoints:** • Mortality at Day 28 and Day 90 • Progression to respiratory support • 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:** • No difference in median number of organ support-free days by Day 21: 0 days in CP arm vs. 3 days in usual care arm (OR 0.97; 95% CrI, 0.82–1.14). **Secondary Outcomes:** • No difference for in-hospital mortality between CP arm (37%) and usual care arm (38%). • No difference in median number of respiratory support-free days: 0 days in CP arm and 2 days in usual care arm. • No difference in median ICU LOS: 21 days in CP arm and 17 days in usual care arm.	**Key Limitations:** • Open-label study • Not all patients in CP arm received CP (86% received CP as per protocol and 95% received some CP) **Interpretation:** • There was no benefit of CP in hospitalized patients with severe COVID-19.

Methods	Results	Limitations and Interpretation
CONCOR-1: Multinational, Open-Label RCT of Convalescent Plasma for Hospitalized Patients With COVID-19 in Canada, the United States, and Brazil[2]		

Key Inclusion Criteria:
• Hospitalized patients receiving supplemental oxygen
• Within 12 days of respiratory symptom onset
Key Exclusion Criteria:
• Imminent or current intubation
Interventions:
• 1–2 units CP (approximately 500 mL) from 1–2 donors (n = 625)
• SOC (n = 313)
Primary Endpoint:
• Intubation or death at Day 30
Key Secondary Endpoints:
• Time to intubation or death by Day 30
• Mortality at Day 30 and Day 90
• ICU LOS by Day 30
• Need for renal dialysis by Day 30
• SAE by Day 30
	Participant Characteristics:
	• Mean age 68 years; 59% men
	• 84% receiving systemic corticosteroids at enrollment
	Primary Outcome:
	• Intubation or death occurred in 32% of patients in CP arm and 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 the CP and SOC arms in:
	  • Time to intubation or death
	  • All-cause mortality (23% in CP arm vs. 21% in SOC arm)
	  • ICU LOS (mean 4.3 days in CP arm vs. 3.7 days in SOC arm)
	  • Need for renal dialysis (1.6% in CP arm vs. 2.0% in SOC arm)
	• More SAEs reported in CP arm (33% vs. 26% in SOC arm)
		Key Limitations:
		• Open-label study
		• Trial stopped after 78% of planned enrollment after meeting prespecified futility criteria for early termination
		Interpretation:
		• There was no benefit of CP in oxygen-dependent, hospitalized COVID-19 patients within 12 days of symptom onset.

RECOVERY Trial: Open-Label RCT of High-Titer Convalescent Plasma in Hospitalized Patients in the United Kingdom[3]		

Key Inclusion Criteria:
• Hospitalized patients with clinically suspected or laboratory-confirmed SARS-CoV-2 infection
Key Exclusion Criteria:
• CP contraindicated
Interventions:
• 2 units high-titer CP (IgG SARS-CoV-2 spike protein ratio ≥6.0), first unit ASAP after randomization, second unit ≥12 hours later the next day (n = 5,795)
• Usual care (n = 5,763)
Primary Endpoint:
• All-cause mortality at Day 28
	Participant Characteristics:
	• Mean age 63.5 years; 64% men
	• 5% on MV
	• 92% received corticosteroids
	Primary Outcomes:
	• No difference between the arms in:
	  • Mortality (24% in each arm).
	  • Mortality in patients without detectable SARS-CoV-2 antibodies (32% in CP arm and 34% in SOC arm).
	Secondary Outcomes:
	• No difference between the arms in:
		Key Limitations:
		• Open-label study
		Interpretation:
		• There was no benefit of CP in hospitalized patients with COVID-19.

Methods	Results	Limitations and Interpretation
RECOVERY Trial: Open-Label RCT of High-Titer Convalescent Plasma in Hospitalized Patients in the United Kingdom[3], continued		
Key Secondary Endpoints: • Time to hospital discharge by Day 28 • Among patients not receiving MV, receipt of MV or death by Day 28	• Proportion of patients discharged (66% in CP arm and 67% in SOC arm). • Proportion of patients who progressed to MV or death (28% in CP arm and 29% in SOC arm).	
PLACID Trial: Open-Label RCT of Convalescent Plasma in Hospitalized Adults With Severe COVID-19 in India[4]		
Key Inclusion Criteria: • Hospitalized patients with moderate, laboratory-confirmed SARS-CoV-2 infection • PaO_2/FiO_2 200–300 mm Hg or respiratory rate >24 breaths/min with SpO_2 ≤93% on room air **Key Exclusion Criteria:** • Critical illness **Interventions:** • 2 doses of 200 mL of CP transfused 24 hours apart (n = 235) • SOC (n = 229) **Primary Endpoint:** • Progression to severe disease (defined as PaO_2/FiO_2 <100 mm Hg) or death within 28 days	**Participant Characteristics:** • Median age 52 years; 76% men • Higher prevalence of DM in CP arm (48%) than SOC arm (38%) **Primary Outcomes:** • No difference in proportion of patients who progressed to severe disease or death between CP arm (19%) and SOC arm (18%) (risk ratio 1.04; 95% CI, 0.71–1.54). • Among patients without detectable SARS-CoV-2 neutralizing antibody titers at baseline (n = 70), no difference in proportion of patients who progressed to severe disease or death in CP arm and SOC arm (30% vs. 25%; risk ratio 1.2; 95% CI, 0.6–2.6).	**Key Limitations:** • Open-label study • SARS-CoV-2 antibody testing not used to select CP; many participants may have received low-titer CP **Interpretation:** • CP use did not reduce progression to severe disease or death in hospitalized patients with moderate COVID-19.
PlasmAr Study: Double-Blind RCT of Convalescent Plasma in Hospitalized Adults in Argentina[5]		
Key Inclusion Criteria: • PCR-confirmed, severe COVID-19 **Key Exclusion Criteria:** • Critical illness **Interventions:** • 1 unit CP with SARS-CoV-2 viral spike-RBD IgG titer ≥1:800 (n = 228) • Placebo (n = 106) **Primary Endpoint:** • Clinical status at 30 days (ordinal score)	**Participant Characteristics:** • Median age 62 years; 68% men • 65% with coexisting condition **Primary Outcome:** • No significant difference between the arms in clinical status at 30 days (OR 0.83; 95% CI, 0.52–1.35; P = 0.46). • 30-day mortality 11% in both arms.	**Key Limitations:** • Small sample size **Interpretation:** • There was no benefit of CP in hospitalized patients with severe COVID-19.

Methods	Results	Limitations and Interpretation
Multicenter, Double-Blind RCT of Convalescent Plasma in Hospitalized Adults With Severe COVID-19 in the United States and Brazil[6]		

Key Inclusion Criteria:
• Severe COVID-19 pneumonia
• SpO_2 ≤94% on room air or requirement of supplemental oxygen, MV, or ECMO
Key Exclusion Criteria:
• >5 days on MV or ECMO
• Severe multiorgan failure
Interventions:
• Single dose of CP with SARS-CoV-2 spike-RBD IgG titer ≥1:400 (n = 150)
• Non-SARS-CoV-2 plasma (control) (n = 73)
Primary Endpoint:
• Clinical status on Day 28 (ordinal score)
Key Secondary Endpoints:
• In-hospital and 28-day mortality
• Time to clinical improvement
• Time to discontinuation of supplemental oxygen
• Time to hospital discharge
	Participant Characteristics:
	• Median age 61 years; 66% men
	• 57% required supplemental oxygen at baseline: 25% high-flow oxygen or NIV and 13% MV or ECMO
	• 81% received corticosteroids
	Primary Outcome:
	• No difference in Day 28 clinical status between the arms (OR 1.5; 95% CI, 0.83–2.68; *P* = 0.18).
	Secondary Outcomes:
	• In-hospital mortality lower in CP arm than control arm (13% vs. 25%; OR 0.44; 95% CI, 0.22–0.91; *P* = 0.034). The difference was no longer significant after adjustment for age, sex, and duration of symptoms.
	• No difference between CP arm and control arm in median time to:
	  • Clinical improvement (5 vs. 7 days).
	  • Discontinuation of supplemental oxygen (6 vs. 7 days).
	  • Hospital discharge (9 vs. 8 days).
		Key Limitations:
		• Small sample size
		• Control arm intervention was blood plasma without SARS-CoV-2 antibodies, therefore not possible to identify potential harm due to plasma infusion
		Interpretation:
		• Although the difference in clinical status on Day 28 between the arms was not statistically significant, lower 28-day mortality in the CP arm suggests potential benefit of CP in hospitalized patients with severe COVID-19.

Double-Blind RCT of Early High-Titer Convalescent Plasma Therapy to Prevent Severe COVID-19 in Nonhospitalized Older Adults in Argentina[7]		
Key Inclusion Criteria: • Nonhospitalized • Aged ≥75 years or aged 65–74 years with ≥1 coexisting condition • Mild COVID-19 with symptoms for <72 hours **Key Exclusion Criteria:** • Severe respiratory disease **Interventions:** • 250 mL of CP with IgG against SARS-CoV-2 spike protein >1:1,000 (n = 80) • Placebo (n = 80)	**Participant Characteristics:** • Mean age 77 years; 38% men • Most with comorbidities **Primary Outcome:** • 16% of patients in CP arm and 31% in placebo arm experienced severe respiratory disease by Day 15 (relative risk 0.52; 95% CI, 0.29–0.94; *P* = 0.03).	**Key Limitations:** • Small sample size • Early termination because COVID-19 cases decreased **Interpretation:** • This trial demonstrated a benefit of CP in older adult outpatients with <72 hours of mild COVID-19 symptoms.

Methods	Results	Limitations and Interpretation
Double-Blind RCT of Early High-Titer Convalescent Plasma Therapy to Prevent Severe COVID-19 in Nonhospitalized Older Adults in Argentina[7], continued		
Primary Endpoint: • Severe respiratory disease, defined as respiratory rate ≥30 breaths/min and/or SpO_2 <93% on room air by Day 15		
C3PO: Multicenter, Single-Blind RCT of High-Titer Convalescent Plasma in the United States[8]		
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 Criteria:** • Need for supplemental oxygen **Interventions:** • 250 mL high-titer CP (median titer 1:641) (n = 257) • Placebo (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 (ordinal score) • All-cause mortality within 30 days • Hospital-free days over 30 days	**Participant Characteristics:** • Median age 54 years; 46% men • More patients with immunosuppression in CP arm (33 [13%]) than in placebo arm (17 [7%]) • More patients with ≥3 risk factors in CP arm (141 [55%]) than in placebo arm (123 [48%]) **Primary Outcomes:** • There was no difference between the arms in the number of patients with disease progression: 77 (30%) in CP arm vs. 81 (32%) in placebo arm (risk difference 1.9%; 95% CrI, -6.0% to 9.8%). • 25 patients (19 in CP 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% of patients in CP arm vs. 30% in placebo arm (risk difference 5.8% [-1.9% to 13.6%]). **Secondary Outcomes:** • 5 patients (1.9%) in CP arm and 1 patient (0.4%) in placebo arm died. • No difference in scores for illness severity or mean number of hospital-free days between the CP and placebo arms.	**Key Limitations:** • Imbalance of patients requiring hospital admission during the index visit included in the primary analysis • Slightly more patients with multiple risk factors, including immunosuppression, in CP arm **Interpretation:** • In outpatients with COVID-19 at high risk of severe disease, use of high-titer CP within 1 week of symptom onset did not prevent disease progression.

Methods	Results	Limitations and Interpretation
Retrospective Evaluation of Convalescent Plasma 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 CP were available for retrospective analysis of antibody titer **Intervention:** • High-titer CP (n = 515), medium-titer CP (n = 2,006), or low-titer CP (n = 561), characterized retrospectively **Primary Endpoint:** • Mortality at 30 days after CP transfusion	**Participant Characteristics:** • 31% aged ≥70 years; 61% men; 48% White, 37% Hispanic/Latinx • 61% in ICU; 33% on MV • 51% received corticosteroids and 31% received RDV **Primary Outcomes:** • Mortality at 30 days after transfusion was 22% in high-titer CP arm, 27% in medium-titer CP arm, and 30% in low-titer CP arm. • Patients in high-titer CP arm had a lower risk of death than those in low-titer CP arm (relative risk 0.75; 95% CI, 0.61–0.93). • Mortality was lower among patients who were not receiving MV before CP transfusion (relative risk 0.66; 95% CI, 0.48–0.91). • Among the patients who were on MV before the CP transfusion, there was no difference in mortality between the high-titer and low-titer arms (relative risk 1.02; 95% CI, 0.78–1.32).	**Key Limitation:** • Lack of untreated control arm **Interpretation:** • The study data are not sufficient to establish the efficacy or safety of COVID-19 CP.

Key: ASAP = as soon as possible; CP = convalescent plasma; DM = diabetes; ECMO = extracorporeal membrane oxygenation; EUA = Emergency Use Authorization; HFNC = high-flow nasal cannula; ICU = intensive care unit; Ig = immunoglobulin; IL = interleukin; LOS = length of stay; MV = mechanical ventilation; NIV = noninvasive 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; PCR = polymerase chain reaction; RBD = receptor binding domain; RCT = randomized controlled trial; RDV = remdesivir; SAE = serious adverse event; SOC = standard of care; SpO_2 = oxygen saturation

References

1. Writing Committee for the REMAP-CAP Investigators, Estcourt LJ, Turgeon AF, et al. Effect of convalescent plasma on organ support-free days in critically ill patients with COVID-19: a randomized clinical trial. *JAMA*. 2021;326(17):1690-1702. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34606578.
2. Begin P, Callum J, Jamula E, et al. Convalescent plasma for hospitalized patients with COVID-19: an open-label, randomized controlled trial. *Nat Med*. 2021;27(11):2012-2024. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34504336.
3. RECOVERY Collaborative Group. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled,

open-label, platform trial. *Lancet*. 2021;397(10289):2049-2059. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34000257.

4. Agarwal A, Mukherjee A, Kumar G, et al. Convalescent plasma in the management of moderate COVID-19 in adults in India: open label Phase II multicentre randomised controlled trial (PLACID Trial). *BMJ*. 2020;371:m3939. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33093056.
5. Simonovich VA, Burgos Pratx LD, Scibona P, et al. A randomized trial of convalescent plasma in COVID-19 severe pneumonia. *N Engl J Med*. 2021;384(7):619-629. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33232588.
6. O'Donnell MR, Grinsztejn B, Cummings MJ, et al. A randomized double-blind controlled trial of convalescent plasma in adults with severe COVID-19. *J Clin Invest*. 2021;131(13). Available at: https://www.ncbi.nlm.nih.gov/pubmed/33974559.
7. Libster R, Perez Marc G, Wappner D, et al. Early high-titer plasma therapy to prevent severe COVID-19 in older adults. *N Engl J Med*. 2021;384(7):610-618. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33406353.
8. Korley FK, Durkalski-Mauldin V, Yeatts SD, et al. Early convalescent plasma for high-risk outpatients with COVID-19. *N Engl J Med*. 2021;385(21):1951-1960. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34407339.
9. Joyner MJ, Carter RE, Senefeld JW, et al. Convalescent plasma antibody levels and the risk of death from COVID-19. *N Engl J Med*. 2021;384(11):1015-1027. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33523609.

Immunoglobulins: SARS-CoV-2 Specific

Last Updated: July 17, 2020

Recommendation

- There is insufficient evidence for the COVID-19 Treatment Guidelines Panel to recommend either for or against **severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunoglobulins** for the treatment of COVID-19.

Rationale

Currently, there are no clinical data on the use of SARS-CoV-2 immunoglobulins. Trials evaluating SARS-CoV-2 immunoglobulins are in development but not yet active and enrolling participants.

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

Concentrated antibody preparations derived from pooled plasma collected from individuals who have recovered from COVID-19 can be manufactured as SARS-CoV-2 immunoglobulin, which could potentially suppress the virus and modify the inflammatory response. The use of virus-specific immunoglobulins for other viral infections (e.g., cytomegalovirus [CMV] immunoglobulin for the prevention of post-transplant CMV infection and varicella zoster immunoglobulin for postexposure prophylaxis of varicella in individuals at high-risk) has proven to be safe and effective; however, there are currently no clinical data on the use of such products for COVID-19. Potential risks may include transfusion reactions. Theoretical risks may include antibody-dependent enhancement of infection.

Clinical Data

There are no clinical data on the use of SARS-CoV-2 immunoglobulins for the treatment of COVID-19. Similarly, there are no clinical data on use of specific immunoglobulin or hyperimmunoglobulin products in patients with severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS).

Considerations in Pregnancy

Pathogen-specific immunoglobulins are used clinically during pregnancy to prevent varicella zoster virus (VZV) and rabies and have also been used in clinical trials of therapies for congenital CMV infection.

Considerations in Children

Hyperimmunoglobulin has been used to treat several viral infections in children, including VZV, respiratory syncytial virus, and CMV; efficacy data on their use for other respiratory viruses is limited.

Table 3c. Characteristics of SARS-CoV-2 Antibody-Based Products

Last Updated: April 1, 2022

- The information in this table is based on data from investigational trials evaluating these products for the treatment or prevention of COVID-19. The table includes dose recommendations from the FDA EUAs for patients who meet specified criteria.
- There are limited or no data on dose modifications for patients with organ failure or those who require extracorporeal devices. Please refer to product labels, when available.
- There are currently not enough data to determine whether certain medications can be safely coadministered with therapies for the treatment or prevention of COVID-19. When using concomitant medications with similar toxicity profiles, consider performing additional safety monitoring.
- The potential additive, antagonistic, or synergistic effects and the safety of using combination therapies for the treatment or prevention of COVID-19 are unknown. Clinicians are encouraged to report AEs to the FDA *Medwatch* program.
- For drug interaction information, please refer to product labels and visit the Liverpool COVID-19 Drug Interactions website.
- For the Panel's recommendations on using the drugs listed in this table, please refer to the Anti-SARS-CoV-2 Monoclonal Antibodies, Therapeutic Management of Nonhospitalized Adults With COVID-19, and Prevention of SARS-CoV-2 Infection sections of the Guidelines.

Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Bamlanivimab Plus Etesevimab (Anti-SARS-CoV-2 Monoclonal Antibodies) *Authorized for the treatment or PEP of COVID-19 under FDA EUA, but distribution has paused because the Omicron VOC has markedly reduced in vitro susceptibility to BAM plus ETE.*				
Dose Recommended in FDA EUA for Treatment and PEP of COVID-19 in Adults and Pediatric Patients Weighing ≥40 kg: • BAM 700 mg plus ETE 1,400 mg as a single IV infusion **Doses Recommended in FDA EUA for Treatment and PEP of COVID-19 in Neonates, Infants, Children, and Adolescents Weighing <40 kg:** • *1–12 kg:* BAM 12 mg/kg plus ETE 24 mg/kg as a single IV infusion	• Nausea • Dizziness • Pruritis • Hypersensitivity, including anaphylaxis and infusion-related reactions • These AEs were observed in multiple trials in which participants received either the authorized doses of BAM and ETE or higher doses of each drug.	• Only for administration in health care settings by qualified health care providers who have immediate access to emergency medical services and medications to treat severe infusion reactions. • Monitor during IV infusion and for ≥1 hour after infusion is completed.	• Drug-drug interactions are unlikely between BAM plus ETE and medications that are renally excreted or that are CYP substrates, inhibitors, or inducers.	**Availability:** • **Distribution of BAM plus ETE has paused** because the Omicron VOC has markedly reduced in vitro susceptibility to BAM plus ETE, and this regimen is not expected to provide clinical benefit. • HHS Public Health Emergency updates on the distribution of BAM plus ETE are available. • A list of clinical trials is available: Bamlanivimab Plus Etesevimab

Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Bamlanivimab Plus Etesevimab (Anti-SARS-CoV-2 Monoclonal Antibodies), continued				
• *>12 kg to 20 kg:* BAM 175 mg plus ETE 350 mg as a single IV infusion • *>20 kg to <40 kg:* BAM 350 mg plus ETE 700 mg as a single IV infusion				
Bebtelovimab (Anti-SARS-CoV-2 Monoclonal Antibody) *Authorized for the treatment of COVID-19 under FDA EUA.*				
Dose Recommended in FDA EUA for Treatment of COVID-19 in Adults and Pediatric Patients Aged ≥12 Years and Weighing ≥40 kg: • BEB 175 mg as an IV injection over at least 30 seconds	• Nausea • Vomiting • Pruritis • Rash • Hypersensitivity, including anaphylaxis and infusion-related reactions	• Only for administration in health care settings by qualified health care providers who have immediate access to emergency medical services and medications to treat severe infusion reactions. • Monitor during IV injection and for ≥1 hour after injection is completed.	• Drug-drug interactions are unlikely between BEB and medications that are renally excreted or that are CYP substrates, inhibitors, or inducers.	**Availability:** • Under the FDA EUA, BEB is available for the treatment of high-risk outpatients with mild to moderate COVID-19.[1] See Anti-SARS-CoV-2 Monoclonal Antibodies for a list of high-risk conditions. • A list of clinical trials is available: Bebtelovimab
Casirivimab Plus Imdevimab (Anti-SARS-CoV-2 Monoclonal Antibodies) *Authorized for the treatment or PEP of COVID-19 under FDA EUA, but distribution has paused because the Omicron VOC has markedly reduced in vitro susceptibility to CAS plus IMD.*				
Dose Recommended in FDA EUA for Treatment and PEP of COVID-19 in Adults and Pediatric Patients Aged ≥12 Years and Weighing ≥40 kg: • CAS 600 mg plus IMD 600 mg as a single IV infusion over 1 hour • IV infusion is the preferred route of administration. However, when IV infusion is not feasible or would delay treatment, CAS 600 mg plus IMD 600 mg can be administered as 4 SUBQ injections (2.5 mL per injection) at 4 different sites. See	• Hypersensitivity, including anaphylaxis and infusion-related reactions • These AEs were observed in multiple trials in which participants received CAS 600 mg plus IMD 600 mg or higher doses of each drug. • Injection site reactions, including ecchymosis and erythema, in clinical trial participants who received CAS plus IMD as SUBQ injections	• Only for administration in health care settings by qualified health care providers who have immediate access to emergency medical services and medications to treat severe infusion reactions. • Monitor during IV infusion or SUBQ injections and for ≥1 hour after infusion or injections are completed.	• Drug-drug interactions are unlikely between CAS plus IMD and medications that are renally excreted or that are CYP substrates, inhibitors, or inducers.	**Availability:** • **Distribution of CAS plus IMD has paused** because the Omicron VOC has markedly reduced in vitro susceptibility to CAS plus IMD, and this regimen is not expected to provide clinical benefit. • HHS Public Health Emergency updates on the distribution of CAS plus IMD are available. • A list of clinical trials is available: Casirivimab Plus Imdevimab

Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Casirivimab Plus Imdevimab (Anti-SARS-CoV-2 Monoclonal Antibodies), continued				
the FDA EUA for detailed information. **Dose Recommended in FDA EUA for PEP for Individuals With Ongoing Exposure to SARS-CoV-2:** • After initial dose, repeat dosing of CAS 300 mg plus IMD 300 mg by SUBQ injections or IV infusion every 4 weeks for duration of ongoing exposure.				
Sotrovimab (Anti-SARS-CoV-2 Monoclonal Antibody) *Authorized for the treatment of COVID-19 under FDA EUA, but distribution has paused in some regions of the United States because the Omicron BA.2 subvariant has markedly reduced in vitro susceptibility to SOT.*				
Dose Recommended in FDA EUA for Treatment of COVID-19 in Adults and Pediatric Patients Aged ≥12 Years and Weighing ≥40 kg: • SOT 500 mg as an IV infusion over 15 minutes for 50 mL bag or over 30 minutes for 100 mL bag	• Rash • Diarrhea • Hypersensitivity, including anaphylaxis and infusion-related reactions	• Only for administration in health care settings by qualified health care providers who have immediate access to emergency medical services and medications to treat severe infusion reactions. • Monitor during IV infusion and for ≥1 hour after infusion is completed.	• Drug-drug interactions are unlikely between SOT and medications that are renally excreted or that are CYP substrates, inhibitors, or inducers.	**Availability:** • **Distribution of SOT has paused in some regions of the United States** because the Omicron BA.2 subvariant has markedly reduced susceptibility to SOT, and SOT is not expected to provide clinical benefit. • HHS Public Health Emergency updates on the distribution of CAS plus IMD are available. • Under the FDA EUA, SOT is available for the treatment of high-risk outpatients with mild to moderate COVID-19.[2] See Anti-SARS-CoV-2 Monoclonal Antibodies for a list of high-risk conditions. • A list of clinical trials is available: Sotrovimab

Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Tixagevimab Plus Cilgavimab (Evusheld) (Anti-SARS-CoV-2 Monoclonal Antibody) *Authorized for PrEP of COVID-19 under FDA EUA.*				
Doses Recommended in FDA EUA for PrEP of COVID-19 in Adults and Pediatric Patients Aged ≥12 Years and Weighing ≥40 kg: • TIX 300 mg plus CIL 300 mg as 2 consecutive 3 mL IM injections • A second dose of TIX 150 mg plus CIL 150 mg as 2 consecutive 1.5 mL IM injections is recommended as soon as possible for patients who previously received TIX 150 mg plus CIL 150 mg.	• Hypersensitivity, 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).	• Use with caution in individuals with thrombocytopenia or any coagulation disorder. • Monitor for ≥1 hour after injection.	• If a person has received a COVID-19 vaccine, TIX plus CIL should be administered ≥2 weeks after vaccination. • Drug-drug interactions are unlikely between TIX plus CIL and medications that are renally excreted or that are CYP substrates, inhibitors, or inducers.	• Under the FDA EUA, TIX plus CIL for PrEP of COVID-19 is available for certain patients at high risk of infection. See Prevention of SARS-CoV-2 Infection for more information.[3] • A list of clinical trials is available: Tixagevimab Plus Cilgavimab
COVID-19 Convalescent Plasma *Authorized for the treatment of COVID-19 under FDA EUA.*				
Dose Recommended in FDA EUA for Treatment of COVID-19: • Per the EUA, consider starting clinical dosing with 1 high-titer COVID-19 CP unit (about 200 mL), with administration of additional CP units based on the prescribing provider's medical judgment and the patient's clinical response.	• TRALI • TACO • Allergic reactions • Anaphylactic reactions • Febrile nonhemolytic reactions • Hemolytic reactions • Hypothermia • Metabolic complications • Transfusion-transmitted infections[4] • Thrombotic events • Theoretical risk of antibody-mediated enhancement of infection and suppressed long-term immunity	• Before administering CP to patients with a history of severe allergic or anaphylactic transfusion reactions, the Panel recommends consulting a transfusion medicine specialist who is associated with the hospital blood bank. • Monitor for transfusion-related reactions. • Monitor vital signs at baseline and during and after transfusion.	• Drug products **should not be added** to the IV infusion line for the blood product.	• The decision to use COVID-19 CP for the treatment of COVID-19 in patients aged <18 years should be based on an individualized assessment of risk and benefit.[5] • In patients with impaired cardiac function and heart failure, it may be necessary to reduce the CP volume or decrease the transfusion rate. **Availability:** • Under the FDA EUA, high-titer COVID-19 CP is available for hospitalized patients with COVID-19.[5] See Convalescent Plasma. • A list of clinical trials is available: COVID-19 Convalescent Plasma

Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
SARS-CoV-2-Specific Immunoglobulin *Not approved by the FDA and not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*				
Dose in Clinical Trials for Treatment of COVID-19: • Dose varies by clinical trial.	• TRALI • TACO • Allergic reactions • Antibody-mediated enhancement of infection • RBC alloimmunization • Transfusion-transmitted infections[4]	• Monitor for transfusion-related reactions. • Monitor vital signs at baseline and during and after transfusion.	• Drug products **should not be added** to the IV infusion line for the blood product.	• A list of clinical trials is available: SARS-CoV-2 Immunoglobulin

Key: AE = adverse event; BAM = bamlanivimab; BEB = bebetelovimab; CAS = casirivimab; CIL = cilgavimab; CP = convalescent plasma; CYP = cytochrome P450; ETE = etesevimab; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; HHS = U.S. Department of Health and Human Services; IM = intramuscular; IMD = imdevimab; IV = intravenous; the Panel = the COVID-19 Treatment Guidelines Panel; PEP = post-exposure prophylaxis; PrEP = pre-exposure prophylaxis; RBC = red blood cell; SOT = sotrovimab; SUBQ = subcutaneous; TACO = transfusion-associated circulatory overload; TIX = tixagevimab; TRALI = transfusion-related acute lung injury; VOC = variant of concern

References

1. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for bebtelovimab. 2022. Available at: https://www.fda.gov/media/156152/download.
2. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of sotrovimab. 2022. Available at: https://www.fda.gov/media/149534/download.
3. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for Evusheld (tixagevimab co-packaged with cilgavimab). 2022. Available at: https://www.fda.gov/media/154701/download.
4. Marano G, Vaglio S, Pupella S, et al. Convalescent plasma: new evidence for an old therapeutic tool? *Blood Transfus*. 2016;14(2):152-157. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26674811.
5. Food and Drug Administration. Fact sheet for health care providers: emergency use authorization (EUA) of COVID-19 convalescent plasma for treatment of coronavirus disease 2019 (COVID-19). 2021. Available at: https://www.fda.gov/media/141478/download.

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

Last Updated: April 21, 2021

Mesenchymal Stem Cells

Mesenchymal stem cells are investigational products that have been studied extensively for broad clinical applications in regenerative medicine[1] and for their immunomodulatory properties.[2] It is hypothesized that mesenchymal stem cells could reduce the acute lung injury and inhibit the cell-mediated inflammatory response induced by SARS-CoV-2.

Recommendation

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

Rationale for Recommendation

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

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

Rationale for Use in COVID-19

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

Clinical Data

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

Clinical Data for COVID-19

A pilot study of intravenous mesenchymal stem cell transplantation in China enrolled 10 patients with confirmed COVID-19 categorized according to the National Health Commission of China criteria as critical, severe, or common type. Seven patients (one with critical illness, four with severe illness, and two with common-type illness) received mesenchymal stem cells; three patients with severe illness

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

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

A double-blind randomized controlled trial investigated the safety and efficacy of hUC-MSC infusions in patients with COVID-19 ARDS. Twenty-four patients were randomized to receive either two infusions of hUC-MSC (prepared at a single site) or placebo on Day 0 and Day 3. The primary endpoints were occurrence of prespecified infusion-associated adverse events within 6 hours of each hUC-MSC infusion; cardiac arrest or death within 24 hours after an infusion; and the incidence of adverse events. Secondary endpoints included survival at 31 days after hUC-MSC infusion and time to recovery.[9]

There were no differences between the arms in the primary safety analysis; however, more deaths occurred in the placebo arm (7 deaths) than in the hUC-MSC arm (2 deaths) by Day 31. Data for one participant in the hUC-MSC arm who died due to a failed intubation was censored from the analysis. Time to recovery was shorter in the hUC-MSC arm than in the placebo arm (HR 0.29; 95% CI, 0.09–0.95). Interpretation of these results is limited by the small sample size and a change in an eligibility criterion from enrolling only individuals on invasive mechanical ventilation to including those receiving high-flow oxygen or on noninvasive ventilation.

Clinical Data for Other Viral Infections

In an open-label study of mesenchymal stem cells for the treatment of H7N9 influenza in China, 17 patients received mesenchymal stem cell treatment plus standard of care, and 44 patients received standard of care only. Three patients (17.6%) in the mesenchymal stem cell arm died versus 24 patients (54.5%) in the standard of care arm. The 5-year follow-up was limited to five patients in the mesenchymal stem cell arm. No safety concerns were identified.[10]

Clinical Trials

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

Adverse Effects

Risks associated with mesenchymal stem cell transfusion appear to be uncommon. The potential risks include the potential for mesenchymal stem cells to multiply or change into inappropriate cell types, product contamination, growth of tumors, infections, thrombus formation, and administration site reactions.[11]

Considerations in Pregnancy

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

Considerations in Children

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

References

1. Samsonraj RM, Raghunath M, Nurcombe V, Hui JH, van Wijnen AJ, Cool SM. Concise review: multifaceted characterization of human mesenchymal stem cells for use in regenerative medicine. *Stem Cells Transl Med*. 2017;6(12):2173-2185. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29076267.
2. Li N,Hua J. Interactions between mesenchymal stem cells and the immune system. *Cell Mol Life Sci*. 2017;74(13):2345-2360. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28214990.
3. Food and Drug Administration. FDA warns about stem cell therapies. 2019. Available at: https://www.fda.gov/consumers/consumer-updates/fda-warns-about-stem-cell-therapies. Accessed January 26, 2021.
4. Food and Drug Administration. Approved cellular and gene therapy products. 2019. Available at: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products. Accessed January 26, 2021.
5. Lukomska B, Stanaszek L, Zuba-Surma E, Legosz P, Sarzynska S,Drela K. Challenges and controversies in human mesenchymal stem cell therapy. *Stem Cells Int*. 2019;2019:9628536. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31093291.
6. Shetty AK. Mesenchymal stem cell infusion shows promise for combating coronavirus (COVID-19)-induced pneumonia. *Aging Dis*. 2020;11(2):462-464. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32257554.
7. Leng Z, Zhu R, Hou W, et al. Transplantation of ACE2(-) mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia. *Aging Dis*. 2020;11(2):216-228. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32257537.
8. Shu L, Niu C, Li R, et al. Treatment of severe COVID-19 with human umbilical cord mesenchymal stem cells. *Stem Cell Res Ther*. 2020;11(1):361. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32811531.
9. Lanzoni G, Linetsky E, Correa D, et al. Umbilical cord mesenchymal stem cells for COVID-19 acute respiratory distress syndrome: A double-blind, Phase 1/2a, randomized controlled trial. *Stem Cells Transl Med*. 2021;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33400390.
10. Chen J, Hu C, Chen L, et al. Clinical study of mesenchymal stem cell treating acute respiratory distress syndrome induced by epidemic Influenza A (H7N9) infection, a hint for COVID-19 treatment. *Engineering (Beijing)*. 2020;6(10):1153-1161. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32292627.
11. Centers for Disease Control and Prevention. Stem cell and exosome products. 2019. Available at: https://www.cdc.gov/hai/outbreaks/stem-cell-products.html. Accessed January 26, 2021.

Immunomodulators Under Evaluation for the Treatment of COVID-19

Last Updated: December 16, 2021

Summary Recommendations
The hyperactive inflammatory response to SARS-CoV-2 infection plays a central role in the pathogenesis of COVID-19. See Therapeutic Management of Hospitalized Adults With COVID-19 for the COVID-19 Treatment Guidelines Panel's (the Panel) recommendations on the use of the following immunomodulators for hospitalized patients according to their disease severity: • Corticosteroids: dexamethasone • Interleukin-6 inhibitors: tocilizumab (or sarilumab) • Janus kinase (JAK) inhibitors: baricitinib (or tofacitinib) There is insufficient evidence for the Panel to recommend either for or against the use of the following immunomodulators for the treatment of COVID-19: • Anakinra • Fluvoxamine • Granulocyte-macrophage colony-stimulating factor inhibitors for hospitalized patients • Inhaled corticosteroids The Panel **recommends against** the use of the following immunomodulators for the treatment of COVID-19, except in a clinical trial: • **Baricitinib plus tocilizumab (AIII)** • **Canakinumab (BIIa)** • **Colchicine** for nonhospitalized patients **(BIIa)** • **Intravenous immunoglobulin (IVIG)** (non-SARS-CoV-2-specific) for the treatment of patients with acute COVID-19 **(AIII)**. This recommendation should not preclude the use of IVIG for multisystem inflammatory syndrome in children (MIS-C) or when it is otherwise indicated. • **Bruton's tyrosine kinase inhibitors** (e.g., **acalabrutinib, ibrutinib, zanubrutinib**) **(AIII)** • **JAK inhibitors** other than **baricitinib** and **tofacitinib** (e.g., **ruxolitinib**) **(AIII)** • **Siltuximab (BIII)** The Panel **recommends against** the use of the following immunomodulators for the treatment of COVID-19: • **Colchicine** for hospitalized patients **(AI)**
Rating of Recommendations: A = Strong; B = Moderate; C = Optional **Rating of Evidence:** I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

Colchicine

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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

For Nonhospitalized Patients With COVID-19

COLCORONA, a large randomized placebo-controlled 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 (NP) swab, a slight reduction in hospitalizations was observed among those who received colchicine.

PRINCIPLE, another randomized, open-label, adaptive-platform trial that evaluated colchicine versus usual care, was stopped for futility when no significant difference in time to first self-reported recovery from COVID-19 between the colchicine and usual care recipients was found.[5]

The PRINCIPLE trial showed no benefit of 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 in 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)**.

For Hospitalized Patients With COVID-19

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

Colchicine in Nonhospitalized Patients With COVID-19

The COLCORONA Trial

The COLCORONA trial was a contactless, double-blind, placebo-controlled, randomized trial in

outpatients who received a diagnosis of COVID-19 within 24 hours of enrollment. Participants were aged ≥70 years or aged ≥40 years with at least 1 of the following risk factors for COVID-19 complications: body mass index ≥30, diabetes mellitus, uncontrolled hypertension, known respiratory disease, heart failure or coronary disease, fever ≥38.4°C within the last 48 hours, dyspnea at presentation, bicytopenia, pancytopenia, or the combination of high neutrophil count and low lymphocyte count. Participants were randomized 1:1 to receive colchicine 0.5 mg twice daily for 3 days and then once daily for 27 days or placebo. The primary endpoint was a composite of death or hospitalization by Day 30; secondary endpoints included components of the primary endpoint, as well as the need for mechanical ventilation by Day 30. 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.[4]

Results

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

Limitations

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

The PRINCIPLE Trial

PRINCIPLE is a randomized, open-label, platform trial that evaluated colchicine in symptomatic, nonhospitalized patients with COVID-19 who were aged ≥65 years or aged ≥18 years with comorbidities or shortness of breath, and who had symptoms for ≤14 days. 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 that they completed online daily; those who did not complete the diaries were contacted by telephone on Days 7, 14, and 29. The investigators developed a prespecified criterion for futility, specifying a clinically meaningful benefit in time to first self-reported recovery as a hazard ratio ≥1.2, corresponding to about 1.5 days of faster recovery in the colchicine arm.

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 SARS-CoV-2 positive test results (156 in the colchicine arm; 1,145 in the usual care arm; and 1,454 in the other treatments arm).
- The trial was stopped early because the criterion for futility was met; 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 of self-reported time to recovery and hospitalizations or death due to COVID-19 among concurrent controls also showed no significant differences between the colchicine and usual care arms.
- There were no statistically significant differences in the secondary outcomes between the colchicine and usual care arms in both the primary analysis population and in subgroups, including subgroups based on symptom duration, baseline disease severity, age, or comorbidities.
- The occurrence of adverse events was similar in the colchicine and usual care arms.

Limitations

- The design of the study was open-label treatment.
- The sample size of the colchicine arm was small.

Colchicine in Hospitalized Patients With COVID-19

The RECOVERY Trial

In the RECOVERY trial, hospitalized patients with COVID-19 were randomized to receive colchicine (1 mg loading dose, followed by 0.5 mg 12 hours later, and 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, 10,603 patients (94%) were receiving corticosteroids.
- The primary endpoint of all-cause mortality at Day 28 occurred in 1,173 of 5,610 participants (21%) in the colchicine arm and 1,190 of 5,730 participants (21%) in the placebo arm (rate ratio 1.01; 95% CI, 0.93–1.10; $P = 0.77$).
- There were no statistically significant differences between the arms for the secondary outcomes of median time to being discharged alive, discharge from the hospital within 28 days, and receipt of 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 one case of rhabdomyolysis.

Limitations

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

The GRECCO-19 Trial

GRECCO-19 was a small, prospective, open-label randomized clinical trial in 105 patients hospitalized with COVID-19 across 16 hospitals in Greece. Patients were assigned 1:1 to receive standard of care with colchicine (1.5 mg loading dose, followed by 0.5 mg after 60 minutes and then 0.5 mg twice daily until hospital discharge or for up to 3 weeks) or standard of care alone.[7]

Results

- Fewer patients in the colchicine arm (1 of 55 patients) than in the standard of care arm (7 of 50 patients) reached the primary clinical endpoint of deterioration in clinical status from baseline by 2 points on a 7-point clinical status scale (OR 0.11; 95% CI, 0.01–0.96).
- Participants in the colchicine group were significantly more likely to experience diarrhea (occurred in 45.5% of participants in the colchicine arm vs. 18.0% in the standard of care arm; $P = 0.003$).

Limitations

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

The results of several small randomized trials and retrospective cohort studies that have evaluated various doses and durations of colchicine in hospitalized patients with COVID-19 have been published in peer-reviewed journals or made available as preliminary, non-peer-reviewed reports.[8-11] Some have shown benefits of colchicine use, including less need for supplemental oxygen, improvements in clinical status on an ordinal clinical scale, and reductions in certain inflammatory markers. In addition, some studies have reported higher discharge rates or fewer deaths among patients who received colchicine than among those who received comparator drugs or placebo. However, the findings of these studies are difficult to interpret due to significant design or methodological limitations, including small sample sizes, open-label designs, and differences in the clinical and demographic characteristics of participants and permitted use of various cotreatments (e.g., remdesivir, corticosteroids) in the treatment arms.

Adverse Effects, Monitoring, and Drug-Drug Interactions

Common adverse effects of colchicine include diarrhea, nausea, vomiting, abdominal cramping and pain, bloating, and loss of appetite. In rare cases, colchicine is associated with serious adverse events, such as neuromyotoxicity and blood dyscrasias. Use of colchicine **should be avoided** in patients with severe renal insufficiency, and patients with moderate renal insufficiency who receive the drug should be monitored for adverse effects. Caution should be used when colchicine is coadministered with drugs that inhibit cytochrome P450 (CYP) 3A4 and/or P-glycoprotein (P-gp) because such use may increase the risk of colchicine-induced adverse effects due to significant increases in colchicine plasma levels. The risk of myopathy may be increased with the concomitant use of certain HMG-CoA reductase inhibitors (e.g., atorvastatin, lovastatin, simvastatin) due to potential competitive interactions mediated by CYP3A4 and P-gp pathways.[12,13] 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.[12,14]

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).

References

1. van Echteld I, Wechalekar MD, Schlesinger N, Buchbinder R, Aletaha D. Colchicine for acute gout. *Cochrane Database Syst Rev*. 2014(8):CD006190. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25123076.
2. Xia M, Yang X, Qian C. Meta-analysis evaluating the utility of colchicine in secondary prevention of coronary artery disease. *Am J Cardiol*. 2021;140:33-38. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33137319.
3. Reyes AZ, Hu KA, Teperman J, et al. Anti-inflammatory therapy for COVID-19 infection: the case for colchicine. *Ann Rheum Dis*. 2021 May;80(5):550-557. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33293273.
4. Tardif JC, Bouabdallaoui N, L'Allier PL, et al. Colchicine for community-treated patients with COVID-19 (COLCORONA): a phase 3, randomised, double-blinded, adaptive, placebo-controlled, multicentre trial. *Lancet Respir Med*. 2021;9(8):924-932. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34051877.
5. PRINCIPLE Trial Collaborative Group, Dorward J, Yu L, et al. Colchicine for COVID-19 in adults in the community (PRINCIPLE): a randomised, controlled, adaptive platform trial. *medRxiv*. 2021;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.09.20.21263828v1.
6. RECOVERY Collaborative Group. Colchicine in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet Respir Med*. 2021;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34672950.
7. Deftereos SG, Giannopoulos G, Vrachatis DA, et al. Effect of colchicine vs standard care on cardiac and inflammatory biomarkers and clinical outcomes in patients hospitalized with coronavirus disease 2019: the GRECCO-19 randomized clinical trial. *JAMA Netw Open*. 2020;3(6):e2013136. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32579195.
8. Brunetti L, Diawara O, Tsai A, et al. Colchicine to weather the cytokine storm in hospitalized patients with COVID-19. *J Clin Med*. 2020;9(9). Available at: https://www.ncbi.nlm.nih.gov/pubmed/32937800.
9. Sandhu T, Tieng A, Chilimuri S, Franchin G. A case control study to evaluate the impact of colchicine on patients admitted to the hospital with moderate to severe COVID-19 infection. *Can J Infect Dis Med Microbiol*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33133323.
10. Lopes MI, Bonjorno LP, Giannini MC, et al. Beneficial effects of colchicine for moderate to severe COVID-19: a randomised, double-blinded, placebo-controlled clinical trial. *RMD Open*. 2021;7(1). Available at: https://www.ncbi.nlm.nih.gov/pubmed/33542047.
11. Salehzadeh F, Pourfarzi F, Ataei S. The impact of colchicine on the COVID-19 patients; a clinical trial. *Research Square*. 2020;Preprint. Available at: https://www.researchsquare.com/article/rs-69374/v1.
12. Colchicine (Colcrys) [package insert]. Food and Drug Administration. 2012. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022352s017lbl.pdf.
13. American College of Cardiology. AHA statement on drug-drug interactions with statins. 2016. Available at: https://www.acc.org/latest-in-cardiology/ten-points-to-remember/2016/10/20/21/53/recommendations-for-management-of-clinically-significant-drug. Accessed November 2, 2021.
14. Indraratna PL, Virk S, Gurram D, Day RO. Use of colchicine in pregnancy: a systematic review and meta-analysis. *Rheumatology (Oxford)*. 2018;57(2):382-387. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29029311.

Corticosteroids

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Multiple randomized trials indicate that systemic corticosteroid therapy improves clinical outcomes and reduces mortality in hospitalized patients with COVID-19 who require supplemental oxygen,[1] presumably by mitigating the COVID-19-induced systemic inflammatory response that can lead to lung injury and multisystem organ dysfunction. There is no observed benefit of systemic corticosteroids in hospitalized patients with COVID-19 who do not require supplemental oxygen.[2] The COVID-19 Treatment Guidelines Panel's (the Panel) recommendations for the use of corticosteroids in hospitalized patients with COVID-19 are based on results from these clinical trials (see Tables 4a and 4b for more information). There are no data to support the use of systemic corticosteroids in nonhospitalized patients with COVID-19.

Recommendations

For Nonhospitalized Patients With COVID-19

- See Therapeutic Management of Nonhospitalized Adults With COVID-19 for the Panel's recommendations on the use of dexamethasone or other systemic corticosteroids in certain nonhospitalized patients.
- There is insufficient evidence for the Panel to recommend either for or against the use of inhaled corticosteroids for the treatment of COVID-19.

For Hospitalized Patients With COVID-19

- See Therapeutic Management of Hospitalized Adults With COVID-19 for the Panel's recommendations on the use of dexamethasone or other systemic corticosteroids in certain hospitalized patients.
- There is insufficient evidence for the Panel to recommend either for or against the use of inhaled corticosteroids for the treatment of COVID-19.

Systemic Corticosteroids in Patients With COVID-19

Nonhospitalized Patients

There are no data to support the use of systemic corticosteroids in nonhospitalized patients with COVID-19. Therefore, the safety and efficacy of systemic corticosteroids in this population have not been established. Generally, systemic corticosteroids are associated with adverse events (e.g., hyperglycemia, neuropsychiatric symptoms, secondary infections), which may be difficult to detect and monitor in an outpatient setting (see General Management of Nonhospitalized Patients With Acute COVID-19 for further information). 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)**.

Hospitalized Patients

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 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.[2] 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.[2] For additional information on the RECOVERY trial, see Table 4a.

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 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, ICU-free days over 28 days, or duration of mechanical ventilation at 28 days.[3] See Table 4a for additional information.

Systemic corticosteroids used in combination with other agents, including other immunomodulators such as tocilizumab (see Interleukin-6 Inhibitors)[4,5] or baricitinib (see Kinase Inhibitors),[6] have demonstrated clinical benefit in subsets of hospitalized patients with COVID-19, especially those with early critical illness and/or with signs of systemic inflammation. For the Panel's recommendations on when to use dexamethasone with another immunomodulator, see Therapeutic Management of Hospitalized Adults With COVID-19.

Please see Tables 4a and 4b for data from clinical trials evaluating corticosteroid use for COVID-19.

Systemic Corticosteroids Other Than Dexamethasone

Systemic corticosteroids other than dexamethasone, including hydrocortisone[7,8] and methylprednisolone,[9,10] 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, if true, suggested a beneficial effect). Therefore, evidence to support the use of hydrocortisone or methylprednisolone for the treatment of COVID-19 is not as strong as 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 (oral or IV)[11] 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 previously studied in patients

with ARDS, dexamethasone lacks mineralocorticoid activity and thus has minimal effect on sodium balance and fluid volume.[12]

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[13] and downregulate expression of the receptors used for cell entry.[14,15] Two open-label randomized controlled trials and 2 double-blind placebo-controlled trials provide additional insights regarding the role of inhaled corticosteroids in outpatients with COVID-19, as described below and in Table 4b.

Recommendation

There is insufficient evidence for the Panel to recommend either for or against the use of inhaled corticosteroids for the treatment of COVID-19.

Rationale

Inhaled budesonide was studied in 2 open-label randomized controlled trials in outpatients with mild symptoms of COVID-19.[16,17] The small STOIC trial suggested that initiation of inhaled budesonide in adult outpatients with mild COVID-19 may reduce the need for urgent care or emergency department assessment or hospitalization.[16] PRINCIPLE, a larger, open-label trial in nonhospitalized patients with COVID-19 at high risk of disease progression, found that use of inhaled budesonide did not affect the rate of hospitalization or death but did reduce the time to self-reported recovery.[18] 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.[19] 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.[20]

The above-described studies of inhaled corticosteroid therapy for outpatients with mild COVID-19 have identified inconsistent effects of the therapy on subsequent hospitalization, and similar placebo-controlled trials have not demonstrated that this therapy results in improvements in symptom resolution. The placebo-controlled studies did not enroll enough patients at high risk of disease progression, and therefore, further studies in this population are needed. For additional information on these trials, see Table 4b.

Monitoring, Adverse Effects, and Drug-Drug Interactions

- Clinicians should closely monitor patients with COVID-19 who are receiving dexamethasone for certain adverse effects (e.g., hyperglycemia, secondary infections, psychiatric effects, avascular necrosis).
- Patients who are receiving inhaled corticosteroids may develop oral candidiasis.
- The use of systemic corticosteroids may increase the risk of opportunistic fungal infections (e.g., mucormycosis, aspergillosis) and reactivation of latent infections (e.g., hepatitis B virus infection, herpesvirus infections, strongyloidiasis, tuberculosis).[21-25]

- Cases of severe and disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with tocilizumab and corticosteroids.[26,27] Many clinicians would initiate empiric antiparasitic treatment (e.g., with ivermectin) with or without serologic testing in patients from areas where *Stronglyloides* is endemic (i.e., tropical, subtropical, or warm temperate areas).[28]
- Using systemic corticosteroids with other immunosuppressants, such as tocilizumab or baricitinib, could theoretically increase the risk of secondary infections. However, this adverse effect has not been reported in clinical trials to date.
- Dexamethasone is a moderate cytochrome P450 (CYP) 3A4 inducer. Therefore, it could reduce the concentration and potential efficacy of concomitant medications that are CYP3A4 substrates. Clinicians should review a patient's medication regimen 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 of 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.[29,30]

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 dexamethasone or other corticosteroids for COVID-19 treatment have not been sufficiently evaluated in pediatric patients and caution is warranted when extrapolating recommendations for adults to patients aged <18 years. The Panel recommends using **dexamethasone** for children with COVID-19 who require high-flow oxygen, noninvasive ventilation, 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 perceived to outweigh the risks. The dexamethasone dosing regimen for pediatric patients is dexamethasone 0.15 mg/kg/dose (maximum dose 6 mg) once daily for up to 10 days. There is insufficient evidence to recommend for or against the use of inhaled corticosteroids for pediatric patients with COVID-19. Corticosteroids are second to IV immunoglobulin as the most used therapy for the treatment of multisystem inflammatory syndrome in children (MIS-C).[31,32] See Special Considerations in Children for more information on the management of MIS-C.

Clinical Trials

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

References

1. WHO Rapid Evidence Appraisal for COVID-19 Therapies Working Group, Sterne JAC, Murthy S, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA*. 2020;324(13):1330-1341. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32876694.
2. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with COVID-19. *N Engl J Med*. 2021;384(8):693-704. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32678530.
3. Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. *JAMA*. 2020;324(13):1307-1316. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32876695.
4. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. 2021;397(10285):1637-1645. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33933206.
5. REMAP-CAP Investigators, Gordon AC, Mouncey PR, et al. Interleukin-6 receptor antagonists in critically ill patients with COVID-19. *N Engl J Med*. 2021;384(16):1491-1502. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33631065.
6. Marconi VC, Ramanan AV, de Bono S, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled Phase 3 trial. *Lancet Respir Med*. 2021; Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34480861.
7. Dequin PF, Heming N, Meziani F, et al. Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19: a randomized clinical trial. *JAMA*. 2020;324(13):1298-1306. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32876689.
8. Angus DC, Derde L, Al-Beidh F, et al. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: the REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. *JAMA*. 2020;324(13):1317-1329. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32876697.
9. Corral-Gudino L, Bahamonde A, Arnaiz-Revillas F, et al. Methylprednisolone in adults hospitalized with COVID-19 pneumonia: an open-label randomized trial (GLUCOCOVID). *Wien Klin Wochenschr*. 2021;133(7-8):303-311. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33534047.
10. Tang X, Feng YM, Ni JX, et al. Early use of corticosteroid may prolong SARS-CoV-2 shedding in non-intensive care unit patients with COVID-19 pneumonia: a multicenter, single-blind, randomized control trial. *Respiration*. 2021;100(2):116-126. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33486496.
11. Czock D, Keller F, Rasche FM, Haussler U. Pharmacokinetics and pharmacodynamics of systemically administered glucocorticoids. *Clin Pharmacokinet*. 2005;44(1):61-98. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15634032.
12. Villar J, Ferrando C, Martinez D, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. *Lancet Respir Med*. 2020;8(3):267-276. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32043986.
13. Matsuyama S, Kawase M, Nao N, et al. The inhaled steroid ciclesonide blocks SARS-CoV-2 RNA replication by targeting the viral replication-transcription complex in cultured cells. *J Virol*. 2020;95(1). Available at: https://www.ncbi.nlm.nih.gov/pubmed/33055254.
14. Finney LJ, Glanville N, Farne H, et al. Inhaled corticosteroids downregulate the SARS-CoV-2 receptor ACE2 in COPD through suppression of type I interferon. *J Allergy Clin Immunol*. 2021;147(2):510-519 e515. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33068560.
15. Peters MC, Sajuthi S, Deford P, et al. COVID-19-related Genes in Sputum Cells in Asthma. Relationship to Demographic Features and Corticosteroids. *Am J Respir Crit Care Med*. 2020;202(1):83-90. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32348692.

16. Ramakrishnan S, Nicolau DV Jr, Langford B, et al. Inhaled budesonide in the treatment of early COVID-19 (STOIC): a Phase 2, open-label, randomised controlled trial. *Lancet Respir Med*. 2021;9(7):763-772. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33844996.
17. PRINCIPLE Collaborative Group, Yu L, Bafadhel M, et al. Inhaled budesonide for COVID-19 in people at higher risk of adverse outcomes in the community: interim analyses from the PRINCIPLE trial. *medRxiv*. 2021;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.04.10.21254672v1.
18. Yu LM, Bafadhel M, Dorward J, et al. Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. *Lancet*. 2021;398(10303):843-855. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34388395.
19. Clemency BM, Varughese R, Gonzalez-Rojas Y, et al. Efficacy of inhaled ciclesonide for outpatient treatment of adolescents and adults with symptomatic COVID-19: a randomized clinical trial. *JAMA Intern Med*. 2021;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34807241.
20. Ezer N, Belga S, Daneman N, et al. Inhaled and intranasal ciclesonide for the treatment of covid-19 in adult outpatients: CONTAIN Phase II randomised controlled trial. *BMJ*. 2021;375:e068060. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34728476.
21. Garg D, Muthu V, Sehgal IS, et al. Coronavirus disease (COVID-19) associated mucormycosis (CAM): case report and systematic review of literature. *Mycopathologia*. 2021;186(2):289-298. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33544266.
22. Moorthy A, Gaikwad R, Krishna S, et al. SARS-CoV-2, uncontrolled diabetes and corticosteroids—an unholy trinity in invasive fungal infections of the maxillofacial region? A retrospective, multi-centric analysis. *J Maxillofac Oral Surg*. 2021:1-8. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33716414.
23. Machado M, Valerio M, Alvarez-Uria A, et al. Invasive pulmonary aspergillosis in the COVID-19 era: An expected new entity. *Mycoses*. 2021;64(2):132-143. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33210776.
24. Chauvet P, Mallat J, Arumadura C, et al. Risk Factors for invasive pulmonary aspergillosis in critically ill patients with coronavirus disease 2019-induced acute respiratory distress syndrome. *Crit Care Explor*. 2020;2(11):e0244. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33205046.
25. Liu J, Wang T, Cai Q, et al. Longitudinal changes of liver function and hepatitis B reactivation in COVID-19 patients with pre-existing chronic hepatitis B virus infection. *Hepatol Res*. 2020;50(11):1211-1221. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32761993.
26. Lier AJ, Tuan JJ, Davis MW, et al. Case report: disseminated strongyloidiasis in a patient with COVID-19. *Am J Trop Med Hyg*. 2020;103(4):1590-1592. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32830642.
27. Marchese V, Crosato V, Gulletta M, et al. Strongyloides infection manifested during immunosuppressive therapy for SARS-CoV-2 pneumonia. *Infection*. 2021;49(3):539-542. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32910321.
28. Stauffer WM, Alpern JD, Walker PF. COVID-19 and dexamethasone: a potential strategy to avoid steroid-related strongyloides hyperinfection. *JAMA*. 2020;324(7):623-624. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32761166.
29. Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. *Pediatrics*. 1972;50(4):515-525. Available at: https://www.ncbi.nlm.nih.gov/pubmed/4561295.
30. Gyamfi-Bannerman C, Thom EA, Blackwell SC, et al. Antenatal betamethasone for women at risk for late preterm delivery. *N Engl J Med*. 2016;374(14):1311-1320. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26842679.
31. Ouldali N, Toubiana J, Antona D, et al. Association of intravenous immunoglobulins plus methylprednisolone vs immunoglobulins alone with course of fever in multisystem inflammatory syndrome in children. *JAMA*.

2021;325(9):855-864. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33523115.

32. Son MBF, Murray N, Friedman K, et al. Multisystem inflammatory syndrome in children - initial therapy and outcomes. *N Engl J Med*. 2021;385(1):23-34. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34133855.

Table 4a. Systemic 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 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 included participants aged 18 years or older.

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 Criterion:
• Physician determination that risks of participation too great based on patient's medical history or an indication for corticosteroid therapy outside of the study
Interventions:
• 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
	• 56% had ≥1 comorbidity; 24% with diabetes
	• 89% with 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 each arm
	• Received tocilizumab or sarilumab: 2% in DEX arm vs. 3% in SOC arm
	Primary Outcome:
	• Mortality at 28 days
	  • All participants: 23% in DEX arm vs. 26% in SOC arm (age-adjusted rate ratio 0.83; 95% CI, 0.75–0.93; P < 0.001).
	  • Participants 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).
	  • Participants 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).
	  • Participants who did not require supplemental oxygen at randomization: 18% in DEX arm vs. 14% in SOC arm (rate ratio 1.19, 95% CI, 0.91–1.55).
		Key Limitations:
		• Open-label study
		• Published data did not include results for key secondary endpoints (e.g., cause-specific mortality, need for renal replacement), AEs, and key subgroups (e.g., patients with comorbidities)
		• Participants who required supplemental oxygen (but not MV) had variable severity. 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 >80 years were preferentially assigned to supplemental oxygen therapy (and not MV)
		• High mortality of this patient population may limit 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, with greatest benefit in those with MV at randomization.
		• No survival benefit of DEX in patients who did not require supplemental oxygen at baseline.

Methods	Results	Limitations and Interpretation
CoDEX: Open-Label RCT of Dexamethasone in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19 in Brazil[2]		
Key Inclusion Criteria: • Confirmed or suspected COVID-19 • Received MV within 48 hours of meeting criteria for moderate to severe ARDS (PaO_2/FiO_2 ≤200 mm Hg) **Key Exclusion Criteria:** • Immunosuppressive drugs in past 21 days • Expected death within 24 hours **Interventions:** • DEX 20 mg IV daily for 5 days, then DEX 10 mg IV daily for 5 days or until ICU discharge (n = 151) • SOC alone (n = 148) **Primary Endpoint:** • Days alive and free from MV by Day 28 **Key Secondary Endpoints:** • All-cause mortality at Day 28 • ICU-free days by Day 28 • Duration of MV by Day 28 • Score on 6-point ordinal scale at Day 15 • SOFA score at 7 days	**Participant Characteristics:** • Mean age: 60 years in DEX arm vs. 63 years in SOC arm • Women: 40% in DEX arm vs. 35% in SOC arm • 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 • None 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 days in DEX arm vs. 4 days in SOC arm ($P = 0.04$). **Secondary Outcomes:** • No differences in arms for Day 28 all-cause mortality (56.3% vs. 61.5%), ICU-free days, and duration of MV, or for Day 15 score on 6-point ordinal scale. • Mean SOFA score at 7 days: 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; $P = 0.01$).	**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 generalizability to populations with a lower baseline mortality • More than one-third of those randomized to 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
COVID STEROID 2: Multinational Blinded RCT of Dexamethasone 12 mg Versus 6 mg in Adults With COVID-19 and Severe Hypoxemia[3]		

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 corticosteroid ≥5 days
• Invasive fungal infection
• Active TB
Interventions:
• DEX 12 mg IV once daily for up to 10 days (n = 503)
• DEX 6 mg IV once daily for up to 10 days (n = 497)
Primary Endpoint:
• Days alive without life support (MV, circulatory support, or kidney replacement therapy) at 28 days
Key Secondary Endpoints:
• Days alive without life support at 90 days
• 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 onset of symptoms to hospitalization: 7 days
	• 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% via NIV; 21% via 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 days alive without life support: 22 days in 12 mg arm vs. 20 days in 6 mg arm (adjusted mean difference 1.3 days; 95% CI, 0.0–2.6; $P = 0.07$).
	Secondary Outcomes:
	• At 90 days:
	  • Median days alive without life support: 84 days in 12 mg arm vs. 80 days in 6 mg arm.
	  • Median days alive and out of hospital: 62 days in 12 mg arm vs. 48 days in 6 mg arm.
	  • Mortality: 32% in 12 mg arm vs. 38% in 6 mg arm (adjusted relative risk 0.87; 99% CI, 0.70–1.07).
	• Mortality at 28 days: 27% in 12 mg arm vs. 32% in 6 mg arm (adjusted relative risk 0.86; 99% CI, 0.68–1.08).
	• 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).
		Key Limitation:
		• The randomized intervention was <10 days in some patients because the trial allowed up to 5 days of DEX before enrollment
		Interpretation:
		• Among patients with COVID-19 and severe hypoxemia, 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
CAPE COVID: Double-Blind RCT of Hydrocortisone Among Critically Ill Patients With COVID-19 in France[4]		

Key Inclusion Criteria:
• 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 infusion of hydrocortisone 200 mg/day for 7 days, then 100 mg/day for 4 days, then 50 mg/day for 3 days; if improvement by Day 4, then 200 mg/day for 4 days, then 100 mg/day for 2 days, then 50 mg/day for 2 days (n = 76)
• Placebo (n = 73)
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, inhaled nitric oxide
• Nosocomial infection by Day 28
• Clinical status on Day 21
	Participant Characteristics:
	• Mean age 62 years; 70% men; median BMI 28
	• 96% with confirmed SARS-CoV-2 infection
	• Median symptom duration: 9–10 days
	• Required MV: 81% at baseline
	• Received vasopressors: 24% in hydrocortisone arm vs. 18% in placebo arm
	• Received RDV and tocilizumab: <3%
	• 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 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 in proportion with nosocomial infection by Day 28
	• Clinical status on Day 21: no difference in arms, but 15% deaths in hydrocortisone arm vs. 27% deaths 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.
		Key Limitations:
		• Underpowered; enrollment stopped after release of data from the RECOVERY trial
		• Limited information about comorbidities
		Interpretation:
		• Hydrocortisone did not reduce treatment failure at Day 21 in patients with COVID-19 and acute respiratory failure, although early termination limited power to detect difference between study arms.

Methods	Results	Limitations and Interpretation
REMAP-CAP: Randomized, Open-Label, Adaptive Trial of Hydrocortisone in Patients With Severe COVID-19[5]		

Key Inclusion Criteria:
• Presumed or confirmed SARS-CoV-2 infection
• ICU admission for respiratory support
Key Exclusion Criteria:
• Presumed imminent death
• Systemic corticosteroid use
• >36 hours since ICU admission
Interventions:
• Hydrocortisone 50 mg IV 4 times daily for 7 days (n = 137)
• Septic shock-based hydrocortisone 50 mg IV 4 times daily for duration of shock (n = 146)
• No hydrocortisone (n = 101)
Primary Endpoint:
• Days free of respiratory and cardiovascular support up to Day 21
Key Secondary Endpoint:
• In-hospital mortality
	Participant Characteristics:
	• Mean age 60 years; 71% men
	• Mean BMI 29.7–30.9
	• 50% to 64% required MV
	Primary Outcomes:
	• No difference in organ support–free days at Day 21 (median 0 days in each group).
	• 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 septic shock-based hydrocortisone arm.
	Key Secondary Outcome:
	• No differences in mortality: 30% in fixed-dose hydrocortisone arm, 36% in septic shock-based hydrocortisone arm, 33% in no hydrocortisone arm.
		Key Limitations:
		• Open-label study
		• Early termination following release of RECOVERY trial results
		Interpretation:
		• Hydrocortisone did not increase support-free days in either the fixed-dose or the shock-dependent group, although early termination limited power to detect differences between study arms.

Single-Blind RCT of Methylprednisolone in Hospitalized Patients With COVID-19 Pneumonia in China[6]		
Key Inclusion Criteria: • Laboratory-confirmed SARS-CoV-2 infection • Chest CT-confirmed pneumonia • Hospitalized on general ward **Key Exclusion Criteria:** • Severe immunosuppression • Corticosteroid use for other diseases **Interventions:** • Methylprednisolone 1 mg/kg/day IV for 7 days (n = 43) • Saline (n = 43)	**Participant Characteristics:** • Mean age 56 years; 48% men • Median 8 days from symptom onset to randomization • At randomization, 71% received oxygen via nasal cannula **Primary Outcome:** • Clinical deterioration at 14 days: 5% in each arm (OR 1.0; 95% CI, 0.134–7.442; $P = 1.00$). **Secondary Outcomes:** • No difference (all $P > 0.05$) between methylprednisolone arm and saline arm for: • Clinical cure at 14 days: 51% vs. 58%	**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 control arms.

Methods	Results	Limitations and Interpretation
Single-Blind RCT of Methylprednisolone in Hospitalized Patients With COVID-19 Pneumonia in China[6], continued		
Primary Endpoint: • Clinical deterioration at 14 days **Key Secondary Endpoints:** • Clinical cure at 14 days • Time to clinical cure • ICU admission • In-hospital mortality • Days hospitalized	• Time to clinical cure: 14 days vs. 12 days • ICU admission: 5% each • In-hospital mortality: 0% vs. 2% • Days hospitalized: 17 days vs. 13 days	

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; IV = intravenous; JAK = Janus kinase; MV = mechanical ventilation; NIV = noninvasive 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; 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

References

1. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with COVID-19. *N Engl J Med*. 2021;384(8):693-704. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32678530.
2. Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. *JAMA*. 2020;324(13):1307-1316. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32876695.
3. COVID Steroid Trial Group, Munch MW, Myatra SN, et al. Effect of 12 mg vs 6 mg of dexamethasone on the number of days alive without life support in adults with COVID-19 and severe hypoxemia: the COVID STEROID 2 randomized trial. *JAMA*. 2021;326(18):1807-1817. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34673895.
4. Dequin PF, Heming N, Meziani F, et al. Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19: a randomized clinical trial. *JAMA*. 2020;324(13):1298-1306. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32876689.
5. Angus DC, Derde L, Al-Beidh F, et al. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: the REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. *JAMA*. 2020;324(13):1317-1329. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32876697.
6. Tang X, Feng YM, Ni JX, et al. Early use of corticosteroid may prolong SARS-CoV-2 shedding in non-intensive care unit patients with COVID-19 pneumonia: a multicenter, single-blind, randomized control trial. *Respiration*. 2021;100(2):116-126. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33486496.

Table 4b. Inhaled Corticosteroids: Selected Clinical Data

Last Updated: December 16, 2021

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

Methods	Results	Limitations and Interpretation
PRINCIPLE: Open-Label RCT of Inhaled Budesonide in Nonhospitalized Patients With COVID-19[1]		
Key Inclusion Criteria: • Aged ≥65 years or aged ≥50 years with comorbidities • PCR-confirmed or suspected COVID-19 • ≤14 days of symptoms **Key Exclusion Criteria:** • Already taking inhaled or systemic corticosteroids • Unable to use an inhaler • Contraindication to inhaled budesonide **Interventions:** • Usual care plus budesonide 800 mcg inhaled twice daily for 14 days (n = 1,069) • Usual care (n = 787) **Primary Endpoints:** • COVID-19-related hospitalization or death up to 28 days from randomization • Time to reported recovery up to 28 days from randomization	**Participant Characteristics:** • Mean age 64.2 years; 52% women; 92% White • 81% with comorbidities • Median time from symptom onset to randomization: 6 days **Primary Outcomes:** • Percentage of patients who were hospitalized or died due to COVID-19 within 28 days: 6.8% in budesonide arm vs. 8.8% in usual care arm (OR 0.75; 95% CrI, 0.55–1.03). • Median time to reported recovery: 11.8 days in budesonide arm vs. 14.7 days in usual care arm (HR 1.21; 95% CrI, 1.08–1.36).	**Key Limitations:** • Open-label trial • Primary endpoint of time to reported recovery based on participant self-report **Interpretation:** • Inhaled budesonide reduced time to reported recovery but not COVID-19-related hospitalization or death. • The clinical significance of self-reported time to recovery in an open-label study is unclear.
STOIC: Open-Label, Phase 2 RCT of Inhaled Budesonide in Nonhospitalized Adults With Early COVID-19[2]		
Key Inclusion Criteria: • Aged ≥18 years • ≤7 days of symptoms **Key Exclusion Criteria:** • Use of inhaled or systemic glucocorticoids in past 7 days • Known allergy or contraindication to budesonide **Interventions:** • Usual care plus budesonide 800 mcg inhaled twice daily until symptom resolution (n = 73)	**Participant Characteristics:** • Mean age 45 years; 58% women • 9% with CVD, 5% with DM • 95% with positive SARS-CoV-2 RT-PCR result • Median time from symptom onset to randomization: 3 days	**Key Limitations:** • Small, open-label trial • Early termination after statistical analysis determined that additional participants would not alter study outcome

Methods	Results	Limitations and Interpretation
STOIC: Open-Label, Phase 2 RCT of Inhaled Budesonide in Nonhospitalized Adults with Early COVID-19[2], continued		
• Usual care (n = 73) **Primary Endpoint:** • COVID-19-related urgent care visit, including ED visit or hospitalization	**Primary Outcomes:** • Median duration of budesonide use: 7 days. • Percentage of patients with COVID-19-related urgent care visit or hospitalization: 1% in budesonide arm vs.14% in usual care arm (relative risk reduction 91%).	**Interpretation:** • In adult outpatients with mild COVID-19, inhaled budesonide may reduce the need for urgent care or ED assessment and/or hospitalization.
Phase 3, Double-Blind RCT of Inhaled Ciclesonide in Nonhospitalized Patients With COVID-19[3]		

Key Inclusion Criteria:
• Aged ≥12 years
• Positive SARS-CoV-2 molecular or antigen diagnostic test result in previous 72 hours
• ≥1 symptom of fever, cough, or dyspnea
Key Exclusion Criteria:
• Taken inhaled or intranasal corticosteroid within 14 days of enrollment or systemic corticosteroid within 90 days of enrollment
• Unable to use an inhaler
Interventions:
• Ciclesonide MDI 160 µg/actuation, 2 actuations twice a day for 30 days (n = 197)
• Placebo MDI twice a day for 30 days (n = 203)
Primary Endpoint:
• Time to alleviation of all COVID-19-related symptoms by Day 30
Key Secondary Endpoints:
• Alleviation of COVID-19-related symptoms by Day 30
• ED visit or hospital admission for COVID-19 by Day 30
• Hospital admission or death by Day 30
	Participant Characteristics:
	• Mean age 43.3 years; 55.3% women; 86.3% White
	• Mean BMI 29.4
	• 22.3% with HTN, 7.5% with type 2 DM
	• Higher rates of DM and asthma in ciclesonide arm
	Primary Outcome:
	• Median time to alleviation of all COVID-19-related symptoms: 19.0 days in ciclesonide arm vs. 19.0 days in placebo arm (HR 1.08; 95% CI, 0.84–1.38).
	Secondary Outcomes:
	• By Day 30, percentage of patients in whom the following outcomes occurred:
	  • Alleviation of COVID-19-related symptoms: 70.6% in ciclesonide arm vs. 63.5% in placebo arm.
	  • Subsequent ED visit or hospital admission for COVID-19: 1.0% in ciclesonide arm vs. 5.4% in placebo arm (OR 0.18; 95% CI, 0.04–0.85).
	  • Hospital admission or death: 1.5% in ciclesonide arm vs. 3.4% in placebo arm (OR 0.45; 95% CI, 0.11–1.84).
	• No deaths by Day 30 in either arm.
		Key Limitations:
		• ED or hospitalization outcome based on small number of events
		• Primary endpoint of time to alleviation of all symptoms based on participant self-report
		Interpretation:
		• Inhaled ciclesonide did not reduce time to reported recovery.
		• The robustness of the conclusion that inhaled ciclesonide reduced COVID-19-related ED visits or hospitalization is uncertain; there were only a small number of events, which is most likely due to the relatively low rate of comorbidities in the study population.

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

References

1. Yu LM, Bafadhel M, Dorward J, et al. Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. *Lancet*. 2021;398(10303):843-855. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34388395.

2. Ramakrishnan S, Nicolau DV, Jr., Langford B, et al. Inhaled budesonide in the treatment of early COVID-19 (STOIC): a Phase 2, open-label, randomised controlled trial. *Lancet Respir Med*. 2021;9(7):763-772. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33844996.
3. Clemency BM, Varughese R, Gonzalez-Rojas Y, et al. Efficacy of inhaled ciclesonide for outpatient treatment of adolescents and adults with symptomatic COVID-19: a randomized clinical trial. *JAMA Intern Med*. 2021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34807241.
4. Ezer N, Belga S, Daneman N, et al. Inhaled and intranasal ciclesonide for the treatment of COVID-19 in adult outpatients: CONTAIN Phase II randomised controlled trial. *BMJ*. 2021;375:e068060. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34728476.

Fluvoxamine

Last Updated: December 16, 2021

Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) that is approved by the Food and Drug Administration (FDA) for the treatment of obsessive-compulsive disorder and is used for other conditions, including depression. Fluvoxamine is not FDA-approved for the treatment of any infection.

Anti-Inflammatory Effect of Fluvoxamine and Rationale for Use in COVID-19

In a murine sepsis model, fluvoxamine was found to bind to the sigma-1 receptor on immune cells, resulting in reduced production of inflammatory cytokines.[1] In an in vitro study of human endothelial cells and macrophages, fluvoxamine reduced the expression of inflammatory genes.[2] Ongoing studies are establishing whether the anti-inflammatory effects of fluvoxamine observed in nonclinical studies also occur in humans and are clinically relevant in the setting of COVID-19.

Recommendation

- There is insufficient evidence for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of fluvoxamine for the treatment of COVID-19.

Rationale

Three randomized trials have studied the use of fluvoxamine for the treatment of nonhospitalized patients with COVID-19. In STOP COVID, a contactless, double-blind randomized placebo-controlled trial conducted in the United States among nonhospitalized adults with mild COVID-19 diagnosed within 7 days of symptom onset, fluvoxamine (100 mg up to 3 times daily for 15 days) reduced clinical deterioration at Day 15.[3] Clinical deterioration was defined as shortness of breath plus oxygen saturation (SpO_2) <92% or hospitalization plus SpO_2 <92%. This was a small study (≤80 participants per arm) with limited cases of clinical deterioration and a short follow-up period. In addition, 24% of participants stopped responding to surveys prior to Day 15.

The subsequent STOP COVID 2, a Phase 3 randomized controlled trial (ClinicalTrials.gov Identifier NCT04668950) that enrolled >700 participants in the United States and Canada, was stopped for futility by a data safety monitoring board after lower than expected case rates and treatment effect were observed.[4]

TOGETHER is an adaptive platform, double-blind randomized placebo-controlled trial conducted in Brazil.[5] Nonhospitalized adults with COVID-19 and a known risk factor for progression to severe disease were randomized to fluvoxamine 100 mg twice daily (n = 741) or placebo (n = 756) for 10 days. Fluvoxamine use was associated with a lower risk of the primary composite outcome of retention in the emergency department for >6 hours or admission to a tertiary hospital (79 of 741 participants [11%] in the fluvoxamine arm vs. 119 of 756 participants [16%] in the placebo arm [relative risk 0.68; 95% CrI, 0.52–0.88]). Of note, 87% of the primary outcome events were hospitalizations. There was no statistically significant difference between study arms for the secondary outcomes of need for hospitalization or time to symptom resolution. There was no significant difference in mortality between study arms in the intention-to-treat (ITT) population (17 of 741 participants [2%] in the fluvoxamine arm vs. 25 of 756 participants [3%] in the placebo arm [OR 0.69; 95% CI, 0.36–1.27]). In a secondary, per-protocol analysis of participants who received >80% of possible doses, death was the outcome for 1 of 548 participants (<1%) in the fluvoxamine arm versus 12 of 618 participants (2%) in the placebo arm (OR 0.09; 95% CI, 0.01–0.47). Participants in the fluvoxamine arm were less likely to present to an emergency setting for COVID-19 for any duration, although this analysis was not prespecified.

Compared with those in the placebo arm, participants who received fluvoxamine were less adherent to therapy and discontinued therapy due to intolerance more often.

While fluvoxamine treatment significantly reduced the primary composite outcome in the TOGETHER trial (i.e., retention in the emergency department for >6 hours or admission to a tertiary hospital), the difference in hospitalizations between arms was not significant.[5] Defining the clinical relevance of the >6 hour emergency department observation time endpoint is difficult, especially its applicability to practice settings in different countries. Moreover, the endpoint has not been used in other studies of interventions for nonhospitalized patients at high risk for hospitalization and death. While a per-protocol analysis found a significant treatment effect for mortality in patients taking >80% of possible doses (assessed by patient self-report), no such benefit was found in the primary ITT analysis. The 80% threshold has no clear justification, and only 74% of participants in the fluvoxamine arm reached this level of adherence. Since per-protocol analyses are not randomized comparisons, they can introduce bias when adherence is associated with factors that influence the outcome; this bias cannot be excluded in this study. Notably, mortality in the placebo arm was substantially higher in those with ≤80% adherence than in those with >80% adherence, suggesting that factors other than adherence differed in the per-protocol population. Finally, including only participants who could tolerate fluvoxamine does not reflect the actual effectiveness of the drug, since intolerance and adherence appeared to be related.

Additional studies are needed to provide more specific, evidence-based guidance on the role of fluvoxamine for the treatment of COVID-19. Further details of the studies discussed are provided in Table 4c.

Adverse Effects, Monitoring, and Drug-Drug Interactions

When fluvoxamine is used to treat psychiatric conditions, the most common adverse effect is nausea, but adverse effects can include other gastrointestinal effects (e.g., diarrhea, indigestion), neurologic effects (e.g., asthenia, insomnia, somnolence, anxiety, headache), and rarely suicidal ideation.

Fluvoxamine is a cytochrome P450 (CYP) 2D6 substrate and a potent inhibitor of CYP1A2 and CYP2C19 and a moderate inhibitor of CYP2C9, CYP2D6, and CYP3A4.[6] Fluvoxamine can enhance the serotonergic effects of other SSRIs or monoamine oxidase inhibitors (MAOIs), resulting in serotonin syndrome; therefore, it should not be used within 2 weeks of receipt of other SSRIs or MAOIs. Fluvoxamine may enhance the anticoagulant effects of antiplatelets and anticoagulants; therefore, patients receiving these drugs should be closely monitored.

Considerations in Pregnancy

Fluvoxamine is not thought to increase the risk of congenital abnormalities; however, the data on its use in pregnancy are limited.[7,8] The association of SSRI use in the late third trimester with a small, increased risk of primary persistent pulmonary hypertension in newborns has not been excluded, although the absolute risk is likely low.[9] The risk of fluvoxamine use in pregnancy for the treatment of COVID-19 should be balanced with the potential benefit.

Considerations in Children

Fluvoxamine is approved by the FDA for the treatment of obsessive-compulsive disorder in children aged ≥8 years.[10] Adverse effects due to SSRI use seen in children are similar to those seen in adults, although children and adolescents appear to have higher rates of behavioral activation and vomiting than adults.[11] There are no data on the use of fluvoxamine for the prevention or treatment of COVID-19 in children.

Clinical Trials

See ClinicalTrials.gov for the latest information on studies of fluvoxamine and COVID-19.

References

1. Rosen DA, Seki SM, Fernandez-Castaneda A, et al. Modulation of the sigma-1 receptor-IRE1 pathway is beneficial in preclinical models of inflammation and sepsis. *Sci Transl Med*. 2019;11(478). Available at: https://www.ncbi.nlm.nih.gov/pubmed/30728287.
2. Rafiee L, Hajhashemi V, Javanmard SH. Fluvoxamine inhibits some inflammatory genes expression in LPS/stimulated human endothelial cells, U937 macrophages, and carrageenan-induced paw edema in rat. *Iran J Basic Med Sci*. 2016;19(9):977-984. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27803785.
3. Lenze EJ, Mattar C, Zorumski CF, et al. Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19: a randomized clinical trial. *JAMA*. 2020;324(22):2292-2300. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33180097.
4. Lenze E. Fluvoxamine for early treatment of COVID-19: the STOP COVID clinical trials. 2021. Available at: https://rethinkingclinicaltrials.org/news/august-20-2021-fluvoxamine-for-early-treatment-of-covid-19-the-stop-covid-clinical-trials-eric-lenze-md/. Accessed December 8, 2021.
5. Reis G, Dos Santos Moreira-Silva EA, Silva DCM, et al. Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: the TOGETHER randomised, platform clinical trial. *Lancet Glob Health*. 2021;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34717820.
6. Hemeryck A, Belpaire FM. Selective serotonin reuptake inhibitors and cytochrome P-450 mediated drug-drug interactions: an update. *Curr Drug Metab*. 2002;3(1):13-37. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11876575.
7. Einarson A, Choi J, Einarson TR, Koren G. Incidence of major malformations in infants following antidepressant exposure in pregnancy: results of a large prospective cohort study. *Can J Psychiatry*. 2009;54(4):242-246. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19321030.
8. Furu K, Kieler H, Haglund B, et al. Selective serotonin reuptake inhibitors and venlafaxine in early pregnancy and risk of birth defects: population based cohort study and sibling design. *BMJ*. 2015;350:h1798. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25888213.
9. Huybrechts KF, Bateman BT, Palmsten K, et al. Antidepressant use late in pregnancy and risk of persistent pulmonary hypertension of the newborn. *JAMA*. 2015;313(21):2142-2151. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26034955.
10. Fluvoxamine maleate tablets [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021519s012lbl.pdf.
11. Safer DJ, Zito JM. Treatment-emergent adverse events from selective serotonin reuptake inhibitors by age group: children versus adolescents. *J Child Adolesc Psychopharmacol*. 2006;16(1-2):159-169. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16553536.

Table 4c. Fluvoxamine: Selected Clinical Data

Last Updated: December 16, 2021

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

Methods	Results	Limitations and Interpretation
TOGETHER: Double-Blind, Adaptive RCT of Fluvoxamine in Nonhospitalized Patients With COVID-19 in Brazil[1]		
Key Inclusion Criteria: • Aged ≥50 years or aged ≥18 years with comorbidities • Laboratory-confirmed SARS-CoV-2 infection • ≤7 days of symptoms **Key Exclusion Criteria:** • Use of an SSRI • Severe mental illness • Cirrhosis, recent seizures, severe ventricular cardia arrythmia **Interventions:** • Fluvoxamine 100 mg PO twice daily for 10 days (n = 741) • Placebo (route, dosing frequency, and duration for some patients may have differed from fluvoxamine) (n = 756) **Primary Endpoint:** • Composite endpoint of emergency setting observation for >6 hours or hospitalization due to progression of COVID-19 within 28 days after randomization **Key Secondary Endpoints:** • Occurrence of COVID-19-related hospitalizations • Time to symptom resolution • Proportion of patients who were adherent to study drugs, defined as receiving >80% of possible doses	**Participant Characteristics:** • Median age 50 years; 58% women; 95% self-identified as mixed race • 13% with uncontrolled HTN; 13% with type 2 DM; 50% with BMI ≥30 kg/m^2 • Mean of 3.8 days from symptom onset to randomization **Primary Outcome:** • Proportion of patients who met the primary composite endpoint: 11% in fluvoxamine arm vs. 16% in placebo arm (relative risk 0.68; 95% CrI, 0.52–0.88) **Secondary Outcomes:** • 87% of clinical events were hospitalizations. • No difference between arms in COVID-19-related hospitalizations: 10% in fluvoxamine arm vs. 13% in placebo arm (OR 0.77; 95% CI, 0.55–1.05) • No difference between arms in time to symptom resolution. • Adherence: 74% in fluvoxamine arm vs. 82% in placebo arm (OR 0.62; 95% CI, 0.48–0.81). 11% in fluvoxamine arm vs. 8% in placebo arm stopped drug due to issues of tolerability. • Mortality (ITT): 2% in fluvoxamine arm vs. 3% in placebo arm (OR 0.68; 95% CI, 0.36–1.27)	**Key Limitations:** • The >6-hour emergency setting observation endpoint has not been used in other studies of interventions for nonhospitalized patients who are at high risk for hospitalization and death • As this was an adaptive platform trial where multiple investigational treatments or placebos were being evaluated simultaneously, not all patients in the placebo arm received a placebo that was matched to fluvoxamine by route of administration, dosing frequency, or duration of therapy • PP analyses are not randomized comparisons, and they introduce bias when adherence is associated with factors that influence the outcome • Adherence was self-reported and not verified **Interpretation:** • Fluvoxamine reduced the proportion of patients who met the composite endpoint of COVID-19-related hospitalization or retention in an emergency setting for >6 hours. • The use of fluvoxamine did not impact the incidence of COVID-19-related hospitalizations.

Methods	Results	Limitations and Interpretation
TOGETHER: Double-Blind, Adaptive RCT of Fluvoxamine in Nonhospitalized Patients With COVID-19 in Brazil[1], continued		
• Mortality in both the primary ITT population and a PP population that included patients who took >80% of the study medication doses	• Mortality (PP): <1% in fluvoxamine arm vs. 2% in placebo arm (OR 0.09; 95% CI, 0.01–0.47)	• It is difficult to define the clinical relevance of the >6-hour emergency setting observation endpoint and apply it to practice settings in different countries. • Fluvoxamine did not have a consistent impact on mortality. • Fluvoxamine did not impact time to symptom resolution.
STOP COVID: Double-Blind RCT of Fluvoxamine in Nonhospitalized Patients With COVID-19 in the United States[2]		

Key Inclusion Criteria:
• Aged ≥18 years
• Positive SARS-CoV-2 PCR result
• ≤7 days of symptoms
Key Exclusion Criteria:
• Immunocompromised
• Unstable medical comorbidities
Interventions:
• Fluvoxamine 50 mg PO for 1 dose, then fluvoxamine 100 mg twice daily, then fluvoxamine 100 mg 3 times daily through Day 15 (n = 80)
• Placebo (n = 72)
Primary Endpoint:
• Clinical deterioration within 15 days of randomization. Clinical deterioration was defined as:
  • Having dyspnea or being hospitalized for dyspnea or pneumonia; *and*
  • Having SpO_2 <92% on room air or requiring supplemental oxygen to attain SpO_2 ≥92%
Key Secondary Endpoint:
• Hospitalization
	Participant Characteristics:
	• Mean age 46 years; 72% women; 25% Black
	• 56% with obesity; 20% with HTN; 17% with asthma
	• Median of 4 days from symptom onset to randomization
	Primary Outcome:
	• Clinical deterioration: 0% in fluvoxamine arm vs. 8.3% in placebo arm (absolute difference 8.7%; 95% CI, 1.8% to 16.4%)
	Secondary Outcome:
	• No patients in fluvoxamine arm and 4 patients in placebo arm were hospitalized.
		Key Limitations:
		• Small sample size
		• Short follow-up period
		• Ascertaining clinical deterioration was challenging because all assessments were done remotely
		• 24% of patients stopped responding to follow-up prior to Day 15 but were included in the final analysis
		Interpretation:
		• Fluvoxamine reduced the proportion of patients who experienced clinical deterioration.
		• Due to significant limitations, it is difficult to draw definitive conclusions about the efficacy of using fluvoxamine to treat COVID-19.

Key: BMI = body mass index; DM = diabetes; HTN = hypertension; ITT = intention-to-treat; the Panel = the COVID-19 Treatment Guidelines Panel; PCR = polymerase chain reaction; PO = oral; PP = per protocol; RCT = randomized controlled trial; SpO_2 = oxygen saturation; SSRI = selective serotonin reuptake inhibitor

References

1. Reis G, Dos Santos Moreira-Silva EA, Silva DCM, et al. Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: the TOGETHER randomised, platform clinical trial. *Lancet Glob Health*. 2021;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34717820.
2. Lenze EJ, Mattar C, Zorumski CF, et al. Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19: a randomized clinical trial. *JAMA*. 2020;324(22):2292-2300. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33180097.

Granulocyte-Macrophage Colony-Stimulating Factor Inhibitors

Last Updated: March 24, 2022

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a myelopoietic growth factor and pro-inflammatory cytokine that plays a central role in a broad range of immune-mediated diseases. GM-CSF, which is secreted by macrophages, T cells, mast cells, natural killer cells, endothelial cells, and fibroblasts, regulates macrophage number and function. It acts as a pro-inflammatory signal, prompting macrophages to launch an immune cascade that ultimately results in tissue damage.[1,2] GM-CSF is believed to be a key driver of lung inflammation in severe and critical COVID-19 pneumonia, operating upstream of other pro-inflammatory cytokines and chemokines.[1-6] Anti-GM-CSF monoclonal antibodies (mAbs) may mitigate inflammation by inhibiting this signaling axis upstream and thus minimizing downstream production of numerous pro-inflammatory mediators involved in the pathogenesis of COVID-19.[7] Gimsilumab, lenzilumab, namilumab, and otilimab target GM-CSF directly, neutralizing the biological function of GM-CSF by blocking the interaction of GM-CSF with its cell surface receptor.[1,8,9] Mavrilimumab targets the alpha subunit of the GM-CSF receptor, blocking intracellular signaling of GM-CSF.[8,10] None of these agents are currently FDA approved for any indication.

Recommendation

- There is insufficient evidence for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of GM-CSF inhibitors for the treatment of hospitalized patients with COVID-19.

Rationale

Clinical data are lacking to definitively establish the potential benefits and risks associated with the use of GM-CSF inhibitors in patients with COVID-19. Data from a double-blind randomized controlled trial of lenzilumab did show a significant improvement in the primary endpoint of ventilator-free survival through Day 28 among those who received the GM-CSF inhibitor.[11] However, preliminary data from a large, double-blind randomized trial of otilimab (primary endpoint: alive and free of respiratory failure at Day 28) and published results of a small, double-blind, randomized trial of mavrilimumab (primary endpoint: proportion alive and off supplemental oxygen at Day 14) did not show a survival benefit for the GM-CSF inhibitors compared to placebo.[12-14] The study populations differed; the lenzilumab and mavrilimumab studies primarily included patients on room air or low-flow oxygen and excluded patients receiving mechanical ventilation, whereas the otilimab study included only patients receiving high-flow oxygen, noninvasive ventilation, or mechanical ventilation. Lenzilumab and mavrilimumab continue to be investigated, whereas clinical development of otilimab for the treatment of COVID-19 has ceased.

Clinical Data for COVID-19

Lenzilumab, mavrilimumab, namilumab, and otilimab have been evaluated in clinical trials in hospitalized adults with SARS-CoV-2 pneumonia.[12-15] Clinical data are not yet published for gimsilumab. The Panel's recommendations are based on the results of the available clinical studies. Selected clinical data on the use of anti-GM-CSF mAbs for the treatment of COVID-19 are summarized in Table 4d.

Clinical Trials

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

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.

References

1. Mehta P, Porter JC, Manson JJ, et al. Therapeutic blockade of granulocyte macrophage colony-stimulating factor in COVID-19-associated hyperinflammation: challenges and opportunities. *Lancet Respir Med*. 2020;8(8):822-830. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32559419.
2. Thwaites RS, Sanchez Sevilla Uruchurtu A, Siggins MK, et al. Inflammatory profiles across the spectrum of disease reveal a distinct role for GM-CSF in severe COVID-19. *Sci Immunol*. 2021;6(57). Available at: https://www.ncbi.nlm.nih.gov/pubmed/33692097.
3. Hamilton JA. GM-CSF in inflammation and autoimmunity. *Trends Immunol*. 2002;23(8):403-408. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12133803.
4. Lotfi N, Thome R, Rezaei N, et al. Roles of GM-CSF in the pathogenesis of autoimmune diseases: an update. *Front Immunol*. 2019;10:1265. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31275302.
5. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31986264.
6. Zhou Y, Fu B, Zheng X, et al. Pathogenic T-cells and inflammatory monocytes incite inflammatory storms in severe COVID-19 patients. *Natl Sci Rev*. 2020;7(6):998-1002. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34676125.
7. De Luca G, Cavalli G, Campochiaro C, et al. GM-CSF blockade with mavrilimumab in severe COVID-19 pneumonia and systemic hyperinflammation: a single-centre, prospective cohort study. *Lancet Rheumatol*. 2020;2(8):e465-e473. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32835256.
8. Lang FM, Lee KM, Teijaro JR, Becher B, Hamilton JA. GM-CSF-based treatments in COVID-19: reconciling opposing therapeutic approaches. *Nat Rev Immunol*. 2020;20(8):507-514. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32576980.
9. Temesgen Z, Assi M, Shweta FNU, et al. GM-CSF neutralization with lenzilumab in severe COVID-19 pneumonia: a case-cohort study. *Mayo Clin Proc*. 2020;95(11):2382-2394. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33153629.
10. Burmester GR, Feist E, Sleeman MA, et al. Mavrilimumab, a human monoclonal antibody targeting GM-CSF receptor-alpha, in subjects with rheumatoid arthritis: a randomised, double-blind, placebo-controlled, phase I, first-in-human study. *Ann Rheum Dis*. 2011;70(9):1542-1549. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21613310.
11. Temesgen Z, Burger CD, Baker J, et al. Lenzilumab in hospitalised patients with COVID-19 pneumonia

(LIVE-AIR): a Phase 3, randomised, placebo-controlled trial. *Lancet Respir Med*. 2021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34863332.

12. Patel J, Beishuizen A, Ruiz XB, et al. A randomized trial of otilimab in severe COVID-19 pneumonia (OSCAR). *medRxiv*. 2021. Available at: https://www.medrxiv.org/content/10.1101/2021.04.14.21255475v1.
13. Temesgen Z, Burger CD, Baker J, et al. Lenzilumab efficacy and safety in newly hospitalized COVID-19 subjects: results from the live-air Phase 3 randomized double-blind placebo-controlled trial. *medRxiv*. 2021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33972949.
14. Cremer PC, Abbate A, Hudock K, et al. Mavrilimumab in patients with severe COVID-19 pneumonia and systemic hyperinflammation (MASH-COVID): an investigator initiated, multicentre, double-blind, randomised, placebo-controlled trial. *Lancet Rheumatol*. 2021;3(6):e410-e418. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33754144.
15. Fisher BA, Veenith T, Slade D, et al. Namilumab or infliximab compared with standard of care in hospitalised patients with COVID-19 (CATALYST): a randomised, multicentre, multi-arm, multistage, open-label, adaptive, Phase 2, proof-of-concept trial. *Lancet Respir Med*. 2021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34922649.
16. Chaulagain CP, Pilichowska M, Brinckerhoff L, Tabba M, Erban JK. Secondary pulmonary alveolar proteinosis in hematologic malignancies. *Hematol Oncol Stem Cell Ther*. 2014;7(4):127-135. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25300566.

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

Last Updated: March 24, 2022

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

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

Methods	Results	Limitations and Interpretation
LIVE-AIR: Double-Blind RCT of Lenzilumab in Hospitalized Patients With Severe COVID-19 Pneumonia in the United States and Brazil[1,2]		
Key Inclusion Criteria: • Hospitalized with SARS-CoV-2 pneumonia • SpO_2 ≤94% on room air or required low-flow supplemental oxygen, HFNC oxygen, or NIV **Key Exclusion Criteria:** • MV or ECMO • Bacterial pneumonia, fungal or viral infection • 48-hour survival not expected • Use of IL-1 inhibitors, IL-6 inhibitors, kinase inhibitors, or mAbs within prior 8 weeks **Interventions:** • 3 doses of lenzilumab 600 mg IV 8 hours apart (n = 236) • Placebo (n = 243) **Primary Endpoint:** • Survival without MV through Day 28 **Key Secondary Endpoints:** • Mortality • Incidence of death or requiring MV or ECMO **Exploratory Endpoint:** • Survival without MV, stratified by baseline CRP	**Participant Characteristics:** • Mean age 61 years; 65% men; 72% White • 55% BMI ≥30 • At baseline: 41% received HFNC oxygen or NIV • 94% received corticosteroids; 72% received RDV; 69% received corticosteroids and RDV • Median CRP 79 mg/L **Primary Outcome:** • Survival without MV through Day 28: 84% in lenzilumab arm vs. 78% in placebo arm (HR 1.54; 95% CI, 1.02–2.32; *P* = 0.040) **Key Secondary Outcomes:** • Mortality: 10% in lenzilumab arm vs. 14% in placebo arm (HR 0.72; 95% CI, 0.42–1.23; *P* = 0.24) • Incidence of death or requiring MV or ECMO: 15% in lenzilumab arm vs. 21% in placebo arm (HR 0.67; 95% CI, 0.41–1.10; *P* = 0.11) **Exploratory Outcome:** • Survival without MV for baseline CRP <150 mg/L: 90% in lenzilumab arm vs. 79% in placebo arm (HR 2.54; 95% CI, 1.46–4.41; *P* = 0.0009)	**Key Limitations:** • Not powered to detect a survival benefit • Access to supportive care differed across study sites **Interpretation:** • Lenzilumab improved ventilator-free survival in participants with hypoxemia who were not receiving MV, with the greatest benefit among those with lower CRP levels.

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

References

1. Temesgen Z, Burger CD, Baker J, et al. Lenzilumab in hospitalised patients with COVID-19 pneumonia (LIVE-AIR): a Phase 3, randomised, placebo-controlled trial. *Lancet Respir Med*. 2021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34863332.
2. Temesgen Z, Kelley CF, Cerasoli F, et al. Early lenzilumab treatment of COVID-19 patients using c-reactive protein as a biomarker improves efficacy: results from the Phase 3 'LIVE-AIR' trial. *medRxiv*. 2022;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.12.30.21267140v1.

3. Cremer PC, Abbate A, Hudock K, et al. Mavrilimumab in patients with severe COVID-19 pneumonia and systemic hyperinflammation (MASH-COVID): an investigator initiated, multicentre, double-blind, randomised, placebo-controlled trial. *Lancet Rheumatol*. 2021;3(6):e410-e418. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33754144.
4. Patel J, Beishuizen A, Ruiz X, et al. A randomized trial of otilimab in severe COVID-19 pneumonia (OSCAR). *medRxiv*. 2021;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.04.14.21255475v1.

Immunoglobulins: Non-SARS-CoV-2 Specific

Last Updated: July 17, 2020

Recommendation

- The COVID-19 Treatment Guidelines Panel **recommends against** the use of non-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-specific **intravenous immunoglobulin (IVIG)** for the treatment of acute COVID-19, except in a clinical trial **(AIII)**. This recommendation **should not preclude** the use of IVIG when otherwise indicated for the treatment of complications that arise during the course of COVID-19.

Rationale for Recommendation

It is unknown whether products derived from the plasma of donors without confirmed SARS-CoV-2 infection contain high titer of SARS-CoV-2 neutralizing antibodies. Furthermore, although other blood components in IVIG may have general immunomodulatory effects, it is unclear whether these theoretical effects will benefit patients with COVID-19.

Clinical Data for COVID-19

This study has not been peer reviewed.

A retrospective, non-randomized cohort study of IVIG for the treatment of COVID-19 was conducted across eight treatment centers in China between December 2019 and March 2020. The study showed no difference in 28-day or 60-day mortality between 174 patients who received IVIG and 151 patients who did not receive IVIG.[1] More patients in the IVIG group had severe disease at study entry (71 patients [41%] with critical status in the IVIG group vs. 32 patients [21%] in the non-IVIG group). The median hospital stay was longer in the IVIG group (24 days) than in the non-IVIG group (16 days), and the median duration of disease was also longer (31 days in the IVIG group vs. 23 days in the non-IVIG group). A subgroup analysis that was limited to the critically ill patients suggested a mortality benefit at 28 days, which was no longer significant at 60 days.

The results of this study are difficult to interpret because of important limitations in the study design. In particular, patients were not randomized to receive either IVIG or no IVIG, and the patients in the IVIG group were older and more likely to have coronary heart disease than those in the non-IVG group. In addition, the IVIG group had a higher proportion of patients with severe COVID-19 disease at study entry. Patients in both groups also received many concomitant therapies for COVID-19.

Considerations in Pregnancy

IVIG is commonly used in pregnancy for other indications such as immune thrombocytopenia with an acceptable safety profile.[2,3]

Considerations in Children

IVIG has been widely used in children for the treatment of a number of conditions. including Kawasaki disease, and is generally safe.[4] IVIG has been used in pediatric patients with COVID-19 and multiorgan inflammatory syndrome in children (MIS-C), especially those with a Kawasaki disease-like presentation, but the efficacy of IVIG in the management of MIS-C is still under investigation.

References

1. Shao Z, Feng Y, Zhong L, et al. Clinical efficacy of intravenous immunoglobulin therapy in critical patients with COVID-19: A multicenter retrospective cohort study. *medRxiv*. 2020;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2020.04.11.20061739v2.
2. Committee on Practice Bulletins—Obstetrics. ACOG practice bulletin No. 207: thrombocytopenia in pregnancy. *Obstet Gynecol*. 2019;133(3):e181-e193. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30801473.
3. Neunert C, Lim W, Crowther M, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood*. 2011;117(16):4190-4207. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21325604.
4. Agarwal S, Agrawal DK. Kawasaki disease: etiopathogenesis and novel treatment strategies. *Expert Rev Clin Immunol*. 2017;13(3):247-258. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27590181.

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 two IL-6 inhibitors, anakinra, interferon beta-1a, and a control group. Participants are eligible for enrollment if they are within 24 hours of receiving respiratory or cardiovascular organ support in the ICU and they have suspected or microbiologically confirmed COVID-19.

Anakinra 300 mg was given intravenously (IV) as a loading dose, followed by anakinra 100 mg IV every 6 hours for 14 days until patients were either free from invasive mechanical ventilation for >24 hours or discharged from the ICU. The primary outcome was measured using an ordinal scale that included a composite of in-hospital mortality and duration of respiratory and cardiovascular organ support at 21 days; all deaths up to 90 days were assigned the worst outcome. The trial used a Bayesian design that allowed the authors to compare nonconcurrently randomized interventions across time periods.[6]

Results

- Of the 2,274 participants who were randomized to one of the arms in the Immune Modulation Therapy domain, 365 individuals were assigned to receive anakinra and included in the analysis, 406 were assigned to the usual care (control) arm, 943 were assigned to receive tocilizumab, and 483 were assigned to receive sarilumab.
- Of those assigned to receive anakinra, 37% were receiving invasive mechanical ventilation at study entry compared with 32% of patients in the other arms. The other patients received oxygen through a high-flow nasal cannula or noninvasive ventilation, with a few exceptions.
- The median number of organ support-free days was similar for patients who received anakinra and

those who received usual care (0 days [IQR 1–15 days] vs. 0 days [IQR -1 to 15 days]). The aOR for organ support-free days was 0.99 for anakinra (95% CrI, 0.74–1.35), with a 46.6% posterior probability of superiority to control. Sixty percent of those who were assigned to receive anakinra survived compared to 63% of those who were assigned to the control arm, with a 43.6% posterior probability that anakinra was superior to usual care.

- The risk of experiencing serious adverse events was similar between the arms.

Limitations

- Patients were not randomized contemporaneously to receive anakinra or usual care; the treatment effect was estimated from an overarching model that mostly included patients who were randomized to receive an IL-6 inhibitor (tocilizumab or sarilumab) or usual care, and patients who were randomized to receive an IL-6 inhibitor or anakinra. Thus, the estimate of the treatment effect is not fully protected by randomization.
- This study had an open-label design.

CORIMUNO-ANA-1

The CORIMUNO-ANA-1 trial randomized 116 hospitalized patients with COVID-19 pneumonia 1:1 to receive either usual care plus anakinra (200 mg IV twice a day on Days 1–3, 100 mg IV twice on Day 4, and 100 mg IV once on Day 5) or usual care alone. Patients were eligible for enrollment if they had laboratory-confirmed SARS-CoV-2 infection with COVID-19 pneumonia and they required >3 L/min of supplemental oxygen. Patients who required high-flow oxygen, ventilation, or ICU admission were excluded. The two coprimary outcomes were the proportion of patients who had died or who needed noninvasive or invasive mechanical ventilation by Day 4 (score of >5 on the WHO-CPS) and the proportion who survived without the need for noninvasive or invasive mechanical ventilation (including high-flow oxygen) by Day 14.[5]

Results

- There was no difference between the anakinra plus usual care arm and the usual care alone arm in the two coprimary outcomes: by Day 4, 36% of patients in the anakinra arm had died or required high-flow oxygen or ventilation compared with 38% in the usual care arm (90% CrI, -17.1 to 12.0, posterior probability of benefit 61%). By Day 14, 47% of patients in the anakinra arm had died or required noninvasive or invasive mechanical ventilation compared to 51% in the usual care arm (median HR 0.97; 90% CrI, 0.62–1.52; posterior probability of benefit 55%).
- Fifty-two percent of patients received corticosteroids at study entry.
- Serious adverse events occurred in 46% of patients in the anakinra arm compared to 38% in the usual care arm; 11 of 59 patients (18.6%) in the anakinra arm experienced bacterial or fungal infections compared to 4 of 55 patients (7.3%) who received usual care.

Limitations

- The limitations of this study include the small sample size, narrow eligibility criteria, and the fact that many patients did not receive current standard-of-care therapy (e.g., corticosteroids, remdesivir).

CAN-COVID

CAN-COVID was a double-blind, placebo-controlled randomized trial of 454 hospitalized patients with COVID-19 who were hypoxemic but not mechanically ventilated and had elevated C-reactive protein (≥ 20 mg/L) or ferritin (≥600 micrograms/L) levels. Patients were randomized 1:1 to receive a single dose of IV canakinumab (450 mg for a body weight of 40 kg to <60 kg, 600 mg for 60–80 kg, and 750

mg for >80 kg) or placebo. The primary outcome was survival without the need for invasive mechanical ventilation from Days 3 through 29.[7]

Results

- There was no statistical difference between the canakinumab arm and placebo arm in the proportion of patients who survived without invasive mechanical ventilation (88.8% vs. 85.7%; $P = 0.29$).
- The number of COVID-19-related deaths at 4 weeks was similar for the two arms (11 of 223 patients [4.9%] in the canakinumab arm vs. 16 of 222 patients [7.2%] in the placebo arm; OR 0.67; 95% CI, 0.30–1.50).
- Forty-one percent of patients in the canakinumab arm and 32% in the placebo arm received dexamethasone.
- Serious adverse events occurred in 16% of patients who received canakinumab and in 20.6% of patients who received placebo.

Limitations

- The use of corticosteroids was unbalanced in this study, with more patients receiving dexamethasone at baseline in the canakinumab arm than in the placebo arm.
- More patients received dexamethasone after the trial was underway in the placebo arm than in the canakinumab arm (22.5% vs. 14.5%), and more patients received tocilizumab in the placebo arm than in the canakinumab arm (8.8% vs. 2.2%).

Other small cohort studies, case-control studies, and case series have reported mixed findings with regard to improvement in outcomes among patients who received anakinra for the treatment of COVID-19.[8-11] The clinical implication of these findings is uncertain due to small sample sizes and unmeasured confounding factors. Therefore, these studies did not substantially influence the Panel's current recommendations for using IL-1 inhibitors.

Clinical Trials

See ClinicalTrials.gov for a list of clinical trials that are evaluating anakinra and canakinumab for the treatment of COVID-19.

Adverse Effects

Headache, nausea, vomiting, and liver enzyme elevations can occur with both anakinra and canakinumab.

Anakinra was not associated with any significant safety concerns when used in clinical trials for the treatment of sepsis.[12-14] Increased rates of infection were reported with prolonged anakinra use in combination with tumor necrosis factor-alpha blockade, but not with short-term use.[15]

Considerations in Pregnancy

The data on using IL-1 inhibitors to treat COVID-19 in pregnant patients are currently limited. The American College of Rheumatology recommends against the use of anakinra during pregnancy.[16] Unintentional first-trimester exposure to anakinra is unlikely to be harmful, given the minimal transfer of monoclonal antibodies across the placenta early in pregnancy.[17]

Considerations in Children

Anakinra has been used in the treatment of severely ill children with rheumatologic conditions, including MAS. The data on the use of anakinra in pediatric patients with acute respiratory distress syndrome or sepsis are limited. Anakinra is rarely used to treat pediatric patients with acute COVID-19, and it has been used in approximately 10% of cases of multisystem inflammatory syndrome in children (MIS-C).[18,19] Anakinra is often included in institutional protocols for the treatment of MIS-C in the United States, and it is mentioned as an option for second-line therapy for refractory MIS-C in national consensus guidelines.[20-22] However, robust data on the effectiveness of anakinra for the treatment of MIS-C are not currently available. Data on using canakinumab in pediatric patients are limited to use in patients with periodic fever syndromes and systemic juvenile idiopathic arthritis. There are no data on its use in pediatric patients with acute COVID-19 or MIS-C. The Panel recommends consulting with a multidisciplinary team when using immunomodulating therapy (which may include anakinra) in children with MIS-C **(AIII)**.

References

1. Shakoory B, Carcillo JA, Chatham WW, et al. Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of macrophage activation syndrome: reanalysis of a prior Phase III trial. *Crit Care Med*. 2016;44(2):275-281. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26584195.
2. Monteagudo LA, Boothby A, Gertner E. Continuous intravenous anakinra infusion to calm the cytokine storm in macrophage activation syndrome. *ACR Open Rheumatol*. 2020;2(5):276-282. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32267081.
3. Anakinra (Kineret) [package insert]. Food and Drug Administration. 2012. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103950s5136lbl.pdf.
4. Kyriazopoulou E, Poulakou G, Milionis H, et al. Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial. *Nat Med*. 2021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34480127.
5. CORIMUNO-19 Collaborative Group. Effect of anakinra versus usual care in adults in hospital with COVID-19 and mild-to-moderate pneumonia (CORIMUNO-ANA-1): a randomised controlled trial. *Lancet Respir Med*. 2021;9(3):295-304. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33493450.
6. The REMAP-CAP Investigators, Derde LPG. Effectiveness of tocilizumab, sarilumab, and anakinra for critically ill patients with COVID-19: the REMAP-CAP COVID-19 immune modulation therapy domain randomized clinical trial. *medRxiv*. 2021;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.06.18.21259133v2.
7. Caricchio R, Abbate A, Gordeev I, et al. Effect of canakinumab vs placebo on survival without invasive mechanical ventilation in patients hospitalized with severe COVID-19: a randomized clinical trial. *JAMA*. 2021;326(3):230-239. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34283183.
8. Aouba A, Baldolli A, Geffray L, et al. Targeting the inflammatory cascade with anakinra in moderate to severe COVID-19 pneumonia: case series. *Ann Rheum Dis*. 2020;79(10):1381-1382. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32376597.
9. Cavalli G, De Luca G, Campochiaro C, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *Lancet Rheumatol*. 2020;2(6):e325-e331. Available at: https://pubmed.ncbi.nlm.nih.gov/32501454/.
10. Huet T, Beaussier H, Voisin O, et al. Anakinra for severe forms of COVID-19: a cohort study. *Lancet Rheumatol*. 2020;2(7):e393-e400. Available at: https://pubmed.ncbi.nlm.nih.gov/32835245/.
11. Kooistra EJ, Waalders NJB, Grondman I, et al. Anakinra treatment in critically ill COVID-19 patients: a prospective cohort study. *Crit Care*. 2020;24(1):688. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33302991.

12. Fisher CJ, Jr., Dhainaut JF, Opal SM, et al. Recombinant human interleukin 1 receptor antagonist in the treatment of patients with sepsis syndrome. Results from a randomized, double-blind, placebo-controlled trial. Phase III rhIL-1ra Sepsis Syndrome Study Group. *JAMA*. 1994;271(23):1836-1843. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8196140.

13. Fisher CJ, Jr., Slotman GJ, Opal SM, et al. Initial evaluation of human recombinant interleukin-1 receptor antagonist in the treatment of sepsis syndrome: a randomized, open-label, placebo-controlled multicenter trial. *Crit Care Med*. 1994;22(1):12-21. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8124953.

14. Opal SM, Fisher CJ Jr, Dhainaut JF, et al. Confirmatory interleukin-1 receptor antagonist trial in severe sepsis: a Phase III, randomized, double-blind, placebo-controlled, multicenter trial. The Interleukin-1 Receptor Antagonist Sepsis Investigator Group. *Crit Care Med*. 1997;25(7):1115-1124. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9233735.

15. Winthrop KL, Mariette X, Silva JT, et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (soluble immune effector molecules [II]: agents targeting interleukins, immunoglobulins and complement factors). *Clin Microbiol Infect*. 2018;24 Suppl 2:S21-S40. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29447987.

16. Sammaritano LR, Bermas BL, Chakravarty EE, et al. 2020 American College of Rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases. *Arthritis Rheumato*l. 2020;72(4):529-556. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32090480.

17. Flint J, Panchal S, Hurrell A, et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-part II: analgesics and other drugs used in rheumatology practice. *Rheumatology (Oxford)*. 2016;55(9):1698-1702. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26750125.

18. Gotzinger F, Santiago-Garcia B, Noguera-Julian A, et al. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. *Lancet Child Adolesc Health*. 2020;4(9):653-661. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32593339.

19. Derespina KR, Kaushik S, Plichta A, et al. Clinical manifestations and outcomes of critically ill children and adolescents with coronavirus disease 2019 in New York City. *J Pediatr*. 2020;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32681989.

20. Dove ML, Jaggi P, Kelleman M, et al. Multisystem inflammatory syndrome in children: survey of protocols for early hospital evaluation and management. *J Pediatr*. 2021;229:33-40. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33075369.

21. Henderson LA, Canna SW, Friedman KG, et al. American College of Rheumatology clinical guidance for multisystem inflammatory syndrome in children associated with SARS-CoV-2 and hyperinflammation in pediatric COVID-19: version 2. *Arthritis Rheumatol*. 2021;73(4):e13-e29. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33277976.

22. Harwood R, Allin B, Jones CE, et al. A national consensus management pathway for paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS): results of a national Delphi process. *Lancet Child Adolesc Health*. 2021;5(2):133-141. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32956615.

Interleukin-6 Inhibitors

Last Updated: December 16, 2021

Interleukin (IL)-6 is a pleiotropic, proinflammatory cytokine produced by a variety of cell types, including lymphocytes, monocytes, and fibroblasts. Infection by SARS-CoV induces a dose-dependent production of IL-6 from bronchial epithelial cells.[1] COVID-19-associated systemic inflammation and hypoxemic respiratory failure can be associated with heightened cytokine release, as indicated by elevated blood levels of IL-6, C-reactive protein (CRP), D-dimer, and ferritin.[2-4] It is hypothesized that modulating IL-6 levels or the effects of IL-6 may reduce the duration and/or severity of COVID-19.

There are 2 classes of Food and Drug Administration (FDA)-approved IL-6 inhibitors: anti-IL-6 receptor monoclonal antibodies (mAbs) (e.g., sarilumab, tocilizumab) and anti-IL-6 mAbs (i.e., siltuximab). These drugs have been evaluated in patients with COVID-19 who have systemic inflammation.

Recommendations

- See Therapeutic Management of Hospitalized Adults With COVID-19 for the COVID-19 Treatment Guidelines Panel's (the Panel) recommendations on the use of IL-6 inhibitors (e.g., sarilumab, tocilizumab) in hospitalized patients who require supplemental oxygen, high-flow oxygen, noninvasive ventilation (NIV), or mechanical ventilation.
- The Panel **recommends against** the use of anti-IL-6 mAb therapy (i.e., **siltuximab**) for the treatment of COVID-19, except in a clinical trial **(BIII)**.

Additional Considerations

- Tocilizumab and sarilumab **should be used with caution** in patients with COVID-19 who have not been adequately represented in clinical trials. This includes patients who are significantly immunosuppressed, particularly those who have recently received other biologic immunomodulating drugs, and patients with any of the following:
  - Alanine transaminase levels >5 times the upper limit of normal
  - A high risk for gastrointestinal perforation
  - An uncontrolled serious bacterial, fungal, or non-SARS-CoV-2 viral infection
  - Absolute neutrophil counts <500 cells/µL
  - Platelet counts <50,000 cells/µL
  - Known hypersensitivity to tocilizumab or sarilumab
- Tocilizumab and sarilumab should only be given in combination with a course of dexamethasone (or an alternative corticosteroid at a dose that is equivalent to dexamethasone 6 mg). See the Corticosteroids section for more information.
- Some clinicians may assess the patient's clinical response to dexamethasone before deciding whether tocilizumab or sarilumab is needed.
- In both the REMAP-CAP and the RECOVERY trials, 29% of patients received a second dose of tocilizumab at the discretion of their treating physician. However, there is currently insufficient evidence to recommend either for or against a second dose of tocilizumab.[5,6]
- Cases of severe and disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with tocilizumab and corticosteroids.[7,8] Many clinicians would initiate empiric treatment (e.g., with the antiparasitic drug ivermectin) with or without serologic testing in patients who are from areas where *Strongyloides* is endemic (i.e., tropical, subtropical, or warm temperate areas).[9]

Rationale

The results of the RECOVERY and REMAP-CAP trials provide consistent evidence that tocilizumab, when coadministered with corticosteroids, offers a modest mortality benefit in certain patients with COVID-19 who are severely ill, who are rapidly deteriorating and have increasing oxygen needs, and who have a significant inflammatory response.[5,6] However, the Panel found it challenging to define the specific patient populations that would benefit from this intervention. If tocilizumab is not available, sarilumab may be used as an alternative because it has demonstrated a similar clinical benefit in improving survival and reducing the duration of organ support in the REMAP-CAP trial.[10] However, the Panel recommends **sarilumab** only when tocilizumab is not available or is not feasible to use **(BIIa)** because the evidence of efficacy for tocilizumab is more extensive than for sarilumab; in addition, sarilumab is currently only approved for use as a subcutaneous (SQ) injection in the United States.

The data on the efficacy of siltuximab in patients with COVID-19 are currently limited.[11]

Anti-Interleukin-6 Receptor Monoclonal Antibodies

Tocilizumab

Tocilizumab is a recombinant humanized anti-IL-6 receptor mAb that is approved by the FDA for use in patients with rheumatologic disorders and cytokine release syndrome induced by chimeric antigen receptor T cell (CAR T-cell) therapy. Tocilizumab can be dosed as an intravenous (IV) infusion or an SQ injection. The IV formulation should be used to treat cytokine release syndrome.[11]

Clinical Data for COVID-19

Clinical data on the use of tocilizumab (and other IL-6 inhibitors) for the treatment of COVID-19, including data from several randomized trials and large observational studies, are summarized in Table 4e.

The initial studies that evaluated the use of tocilizumab for the treatment of COVID-19 produced conflicting results. Many of these trials were limited by low power, heterogenous populations, and/or a low frequency of concomitant use of corticosteroids (now the standard of care for patients with severe COVID-19).[12-16]

Subsequently, in the setting of background corticosteroid therapy, the 2 largest randomized controlled trials evaluating tocilizumab, REMAP-CAP and RECOVERY, both reported a mortality benefit of tocilizumab in certain patients, including patients exhibiting rapid respiratory decompensation associated with an inflammatory response. REMAP-CAP enrolled critically ill patients who were within 24 hours of receiving respiratory support in an intensive care unit. The participants were randomized to receive open-label tocilizumab or usual care. In-hospital mortality was 28% in the tocilizumab arm and 36% in the usual care arm.[5] The RECOVERY trial enrolled hospitalized patients with COVID-19 into an open-label platform trial that included several treatment options.[6] A subset of all trial participants who had hypoxemia and CRP levels ≥75 mg/L were offered enrollment into a second randomization that evaluated tocilizumab versus usual care. In this subgroup, the 28-day mortality was 31% in the tocilizumab arm and 35% in the usual care arm. For additional findings from the REMAP-CAP and RECOVERY trials and the rationale for using tocilizumab in certain hospitalized patients who are exhibiting rapid respiratory decompensations due to COVID-19, see Therapeutic Management of Hospitalized Adults With COVID-19.

In contrast to the REMAP-CAP and RECOVERY trials, the REMDACTA trial did not find a mortality benefit of tocilizumab. The trial randomized hospitalized COVID-19 patients, most of whom required NIV or high-flow oxygen support, to receive tocilizumab or placebo. All the participants received

remdesivir and most received corticosteroids. Tocilizumab use did not reduce 28-day mortality (18% in the tocilizumab arm and 20% in the placebo arm).[17]

Despite this conflicting evidence, the Panel's recommendations for using tocilizumab are based on the collective evidence from the clinical trials reported to date (see Table 4e).

Clinical Trials

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

Adverse Effects

The primary laboratory abnormalities reported with tocilizumab treatment are elevated liver enzyme levels that appear to be dose dependent. Neutropenia or thrombocytopenia are uncommon. In randomized trials, no excess secondary infections were seen among patients who received combination therapy compared to control patients. Additional adverse effects of tocilizumab, such as serious infections (e.g., tuberculosis [TB], bacterial or fungal infections) and bowel perforation, have been reported.[18]

Considerations in Pregnancy

There are insufficient data to determine whether there is a tocilizumab-associated risk for major birth defects or miscarriage. mAbs are actively transported across the placenta as pregnancy progresses (with the greatest transfer occurring during the third trimester), and this may affect immune responses in the exposed fetus. Given the paucity of data, current recommendations advise against the use of tocilizumab during pregnancy.[19] Whether to use tocilizumab during pregnancy should be a joint decision between the pregnant individual and their health care provider, and the decision-making process should include a discussion of the potential risks and benefits.

Considerations in Children

There are no systematic observational or randomized controlled trial data on the effectiveness of tocilizumab for the treatment of acute COVID-19 in pediatric patients or multisystem inflammatory syndrome in children (MIS-C). Tocilizumab has been used for children with cytokine release syndrome associated with CAR T-cell therapy and systemic and polyarticular juvenile idiopathic arthritis.[20] There is insufficient evidence for the Panel to recommend either for or against the use of tocilizumab in hospitalized children with COVID-19 or MIS-C.

Drug Availability

On June 24, 2021, the FDA issued an Emergency Use Authorization (EUA) for the use of tocilizumab in combination with corticosteroids in hospitalized adults and children aged ≥2 years with COVID-19 who require supplemental oxygen, NIV, mechanical ventilation, or extracorporeal membrane oxygenation.[20] Per this EUA, if a patient's clinical signs or symptoms worsen or do not improve after the first dose of tocilizumab, 1 additional infusion of tocilizumab may be administered at least 8 hours after the initial IV infusion. If there is a local or regional shortage of tocilizumab, sarilumab can be used as an alternative (see Therapeutic Management of Hospitalized Adults With COVID-19).[10]

Sarilumab

Sarilumab is a recombinant humanized anti-IL-6 receptor mAb that is approved by the FDA for use in patients with rheumatoid arthritis. It is available as an SQ formulation and is not approved for the treatment of cytokine release syndrome.

Clinical Data for COVID-19

The clinical data on the use of sarilumab as a treatment for COVID-19 are summarized in Table 4e.

An adaptive Phase 2 and 3 double-blind randomized (2:2:1) placebo-controlled trial compared the efficacy and safety of sarilumab 400 mg IV and sarilumab 200 mg IV to placebo in hospitalized patients with COVID-19 (ClinicalTrials.gov Identifier NCT04315298). Results from this trial did not support a clinical benefit of sarilumab in hospitalized patients receiving supplemental oxygen.[21]

A similar adaptive design study in the United States in patients with severe and critical COVID-19 also failed to show a benefit of sarilumab. In this placebo-controlled trial, there was a reduction in mortality among the sarilumab recipients with critical COVID-19 pneumonia who required mechanical ventilation and received corticosteroids at baseline. However, due to the small sample size, this result was not statistically significant.[22] In the REMAP-CAP trial, the efficacy results for sarilumab were similar to those for tocilizumab. Compared to the patients in the standard of care arm (n = 418), those in the sarilumab arm (n = 485) had more organ support-free days (OR 1.50; 95% CrI, 1.13–2.00) and a greater likelihood of survival while hospitalized (OR 1.51; 95% CrI, 1.06–2.20). A notable limitation to the sarilumab findings in the REMAP-CAP trial is that patients in the standard of care arm were enrolled earlier in the pandemic than those in the sarilumab arm: randomization closed on November 2020 for the standard of care arm and continued through April 2021 for the sarilumab arm.[10]

Clinical Trials

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

Adverse Effects

The primary laboratory abnormalities that have been reported with sarilumab treatment are transient and/or reversible elevations in liver enzyme levels that appear to be dose dependent and rare occurrences of neutropenia and thrombocytopenia. Additional adverse effects, such as serious infections (e.g., TB, bacterial or fungal infections) and bowel perforation, have been reported, but only with long-term use of sarilumab.

Considerations in Pregnancy

There are insufficient data to determine whether there is a sarilumab-associated risk for major birth defects or miscarriage. mAbs are actively transported across the placenta as pregnancy progresses (with the greatest transfer occurring during the third trimester), and this may affect immune responses in the exposed fetus.

Considerations in Children

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

Drug Availability

The IV formulation of sarilumab is not approved by the FDA, but in a clinical trial, a single SQ dose (using the prefilled syringe, not the prefilled pen) of sarilumab 400 mg was reconstituted in 100 cc 0.9% NaCl and given as an IV infusion over a 1-hour period.

Anti-Interleukin-6 Monoclonal Antibody

Siltuximab

Siltuximab is a recombinant human-mouse chimeric mAb that binds IL-6 and is approved by the FDA for use in patients with multicentric Castleman disease. Siltuximab prevents the binding of IL-6 to both soluble and membrane-bound IL-6 receptors, inhibiting IL-6 signaling. Siltuximab is dosed as an IV infusion.

Clinical Data for COVID-19

There are limited data on the efficacy of siltuximab in patients with COVID-19.[23] There are no data describing clinical experiences using siltuximab for patients with other novel coronavirus infections (i.e., severe acute respiratory syndrome [SARS], Middle East respiratory syndrome [MERS]).

Clinical Trials

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

Adverse Effects

The primary adverse effects reported for siltuximab have been related to rash. Additional adverse effects (e.g., serious bacterial infections) have been reported only with long-term dosing of siltuximab once every 3 weeks.

Considerations in Pregnancy

There are insufficient data to determine whether there is a siltuximab-associated risk for major birth defects or miscarriage. mAbs are transported across the placenta as pregnancy progresses (with the greatest transfer occurring during the third trimester), and this may affect immune responses in the exposed fetus.

Considerations in Children

The safety and efficacy of siltuximab have not been established in pediatric patients.

References

1. Yoshikawa T, Hill T, Li K, Peters CJ, Tseng CT. Severe acute respiratory syndrome (SARS) coronavirus-induced lung epithelial cytokines exacerbate SARS pathogenesis by modulating intrinsic functions of monocyte-derived macrophages and dendritic cells. *J Virol*. 2009;83(7):3039-3048. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19004938.
2. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32171076.
3. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31986264.
4. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China. *Clin Infect Dis*. 2020;71(15):769-777. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32176772.
5. REMAP-CAP Investigators, Gordon AC, Mouncey PR, et al. Interleukin-6 receptor antagonists in critically ill patients with COVID-19. *N Engl J Med*. 2021;384(16):1491-1502. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33631065.
6. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. 2021;397(10285):1637-1645. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33933206.
7. Lier AJ, Tuan JJ, Davis MW, et al. Case report: disseminated strongyloidiasis in a patient with COVID-19. *Am J Trop Med Hyg*. 2020;103(4):1590-1592. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32830642.
8. Marchese V, Crosato V, Gulletta M, et al. Strongyloides infection manifested during immunosuppressive therapy for SARS-CoV-2 pneumonia. *Infection*. 2021;49(3):539-542. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32910321.
9. Stauffer WM, Alpern JD, Walker PF. COVID-19 and dexamethasone: a potential strategy to avoid steroid-

related strongyloides hyperinfection. *JAMA*. 2020;324(7):623-624. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32761166.

10. The REMAP-CAP Investigators, Derde LPG. Effectiveness of tocilizumab, sarilumab, and anakinra for critically ill patients with COVID-19: the REMAP-CAP COVID-19 immune modulation therapy domain randomized clinical trial. *medRxiv*. 2021;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.06.18.21259133v2.
11. Le RQ, Li L, Yuan W, et al. FDA approval summary: tocilizumab for treatment of chimeric antigen receptor T cell-induced severe or life-threatening cytokine release syndrome. *Oncologist*. 2018;23(8):943-947. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29622697.
12. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of tocilizumab in patients hospitalized with COVID-19. *N Engl J Med*. 2020;383(24):2333-2344. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33085857.
13. Gupta S, Wang W, Hayek SS, et al. Association between early treatment with tocilizumab and mortality among critically ill patients with COVID-19. *JAMA Intern Med*. 2021;181(1):41-51. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33080002.
14. Hermine O, Mariette X, Tharaux PL, et al. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: a randomized clinical trial. *JAMA Intern Med*. 2021;181(1):32-40. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33080017.
15. Salama C, Han J, Yau L, et al. Tocilizumab in patients hospitalized with COVID-19 pneumonia. *N Engl J Med*. 2021;384(1):20-30. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33332779.
16. Rosas IO, Brau N, Waters M, et al. Tocilizumab in hospitalized patients with severe COVID-19 pneumonia. *N Engl J Med*. 2021;384(16):1503-1516. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33631066.
17. Rosas IO, Diaz G, Gottlieb RL, et al. Tocilizumab and remdesivir in hospitalized patients with severe COVID-19 pneumonia: a randomized clinical trial. *Intensive Care Med*. 2021;47(11):1258-1270. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34609549.
18. Charan J, Dutta S, Kaur R, et al. Tocilizumab in COVID-19: a study of adverse drug events reported in the WHO database. *Expert Opin Drug Saf*. 2021;20(9):1125-1136. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34162299.
19. Sammaritano LR, Bermas BL, Chakravarty EE, et al. 2020 American College of Rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases. *Arthritis Rheumatol*. 2020;72(4):529-556. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32090480.
20. Food and Drug Administration. Letter of authorization: EUA for tocilizumab (Actemra) for the treatment of coronavirus disease 2019 (COVID-19). 2021. Available at: https://www.fda.gov/media/150319/download.
21. Lescure FX, Honda H, Fowler RA, et al. Sarilumab in patients admitted to hospital with severe or critical COVID-19: a randomised, double-blind, placebo-controlled, Phase 3 trial. *Lancet Respir Med*. 2021;9(5):522-532. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33676590.
22. Sivapalasingam S, Lederer DJ, Bhore R, et al. Efficacy and safety of sarilumab in hospitalized patients with COVID-19: a randomized clinical trial. *Clin Infect Dis*. 2022;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35219277.
23. Gritti G, Raimondi F, Ripamonti D, et al. IL-6 signalling pathway inactivation with siltuximab in patients with COVID-19 respiratory failure: an observational cohort study. *medRxiv*. 2020;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2020.04.01.20048561v4.

Table 4e. Interleukin-6 Inhibitors: 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 IL-6 inhibitors. The studies summarized below are those that have had the greatest impact on the Panel's recommendations.

Methods	Results	Limitations and Interpretation
RECOVERY Trial: Open-Label RCT of Tocilizumab and Usual Care in Hospitalized Patients With COVID-19[1]		

Key Inclusion Criteria:
• SpO_2 <92% on room air or receipt of supplemental oxygen
• CRP ≥75 mg/L
Key Exclusion Criteria:
• Non-SARS-CoV-2 infection
Interventions:
• Single weight-based dose of tocilizumab (maximum 800 mg) and possible second dose (n = 2,022)
• Usual care (n = 2,094)
Primary Endpoint:
• 28-day all-cause mortality
Key Secondary Endpoints:
• Time to discharge alive within 28 days
• Among those not on MV at enrollment, receipt of MV or death within 28 days
	Participant Characteristics:
	• Mean age 63.6 years; 67% men; 76% White
	• 95% had 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:
	• Day 28 mortality was lower in tocilizumab arm than in usual care arm (31% vs. 35%; rate ratio 0.85; 95% CI, 0.76–0.94; $P = 0.003$).
	• Among those who required MV at baseline, Day 28 mortality was similar between arms (49% in tocilizumab arm vs. 51% in usual care arm; risk ratio 0.93; 95% CI, 0.74–1.18).
	Secondary Outcomes:
	• Proportion of patients discharged alive within 28 days was greater in tocilizumab arm than usual care arm (57% vs. 50%; rate ratio 1.22; 95% CI, 1.12–1.33; $P < 0.0001$).
	• Proportion of patients not on MV at baseline who died or required MV within 28 days was lower in tocilizumab arm than usual care arm (35% vs. 42%; rate ratio 0.84; 95% CI, 0.77–0.92; $P < 0.0001$).
		Key Limitations:
		• Arbitrary enrollment cut off at CRP ≥75 mg/L
		• Difficult to define exact subset of patients in RECOVERY cohort who were subsequently selected for secondary randomization/tocilizumab trial
		Interpretation:
		• Among hospitalized COVID-19 patients with hypoxemia and elevated CRP, tocilizumab was associated with reduced all-cause mortality and shorter time to discharge.

Methods	Results	Limitations and Interpretation
REMAP-CAP: Open-Label, Adaptive-Platform RCT of Tocilizumab and Sarilumab in Patients With COVID-19[2,3]		

Key Inclusion Criteria:
• ICU admission
• Suspected or laboratory-confirmed COVID-19
• Receipt of MV, NIV, or cardiovascular support
Key Exclusion Criteria:
• >24 hours since ICU admission
• Presumption of imminent death
• Immunosuppression
• ALT >5 times ULN
Interventions:
• Single dose of tocilizumab 8 mg/kg IV and possible second dose in 12–24 hours, plus SOC (n = 952)
• Single dose of sarilumab 400 mg IV plus SOC (n = 485)
• SOC (n = 406)
Randomization:
• Adaptative randomization. Patients were randomized to receive SOC only, SOC plus tocilizumab, or SOC plus sarilumab based on provider preference, availability, or adaptive probability. SOC arm was closed in November 2020 (n = 366 for tocilizumab, n = 48 for sarilumab, n = 412 for SOC).
• After November 2020, patients were randomized mostly to receive tocilizumab, sarilumab, or anakinra until April 10, 2021.
Primary Endpoint:
• Composite ordinal endpoint of in-hospital mortality and organ support-free days to Day 21
	Participant Characteristics:
	• Mean age 60 years; 69% men; 75% White
	• 86% had PCR-confirmed SARS-CoV-2 infection
	• Median time from ICU admission until enrollment was 14 hours
	• At baseline:
	  • 67% on HFNC oxygen or NIV
	  • 33% on MV
	  • 67% on corticosteroids in SOC arm, 82% in tocilizumab arm, and 89% in sarilumab arm
	Primary Outcomes
	Tocilizumab Versus SOC:
	• Median number of organ support-free days was 7 in tocilizumab arm and 0 in SOC arm.
	• Median adjusted OR for ordinal scale was 1.46 (95% CrI, 1.13–1.87).
	• In highest CRP tercile, aOR was 1.87 (95% CrI, 1.35–2.59).
	• Outcomes were consistent across subgroups according to oxygen requirement at baseline.
	Sarilumab Versus SOC:
	• Median number of organ support-free days was 9 in sarilumab arm and 0 in SOC arm.
	• Median adjusted OR for ordinal scale was 1.50 (95% CrI, 1.13–2.00).
	• In highest CRP tercile, aOR was 1.85 (95% CrI, 1.24–2.69).
	• Outcomes were consistent across subgroups according to oxygen requirements at study entry.
		Key Limitation:
		• Enrollment in tocilizumab and sarilumab arms was partially nonconcurrent with SOC arm; while the comparisons to SOC arm were adjusted for time period, there is a possibility of bias
		Interpretation:
		• Among patients with respiratory failure who were within 24 hours of ICU admission, the tocilizumab and sarilumab arms had higher rates of in-hospital survival and shorter durations of organ support than the SOC arm.
		• The treatment effect appeared to be strongest in the highest CRP tercile.
		• Tocilizumab and sarilumab were similarly effective, with a 99% probability of noninferiority of sarilumab.

Methods	Results	Limitations and Interpretation
REMAP-CAP: Open-Label, Adaptive-Platform RCT of Tocilizumab and Sarilumab in Patients With COVID-19[2,3], continued		
Key Secondary Endpoint: • In-hospital survival	**Secondary Outcomes** *Tocilizumab Versus SOC:* • In-hospital survival was 66% in tocilizumab arm and 63% in SOC arm (aOR 1.42; 95% CrI, 1.05–1.93). *Sarilumab Versus SOC:* • In-hospital survival was 67% in sarilumab arm and 63% in SOC arm (aOR 1.51; 95% CrI, 1.06–2.20).	
COVACTA: Double-Blind RCT of Tocilizumab in Hospitalized Patients With COVID-19[4]		
Key Inclusion Criteria: • PCR-confirmed SARS-CoV-2 infection • Hypoxemia • Bilateral chest infiltrates **Key Exclusion Criteria:** • Death imminent • Active infection other than SARS-CoV-2 **Interventions:** • Single dose of tocilizumab 8 mg/kg and possible second dose, plus SOC (n = 294) • Placebo plus SOC (n = 144) **Primary Endpoint:** • Day 28 clinical status (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 • 14% on MV • 25% with multiorgan failure • 36% in tocilizumab arm and 55% in placebo arm received corticosteroids at entry or during follow-up **Primary Outcome:** • No significant difference between arms in clinical status at Day 28. **Secondary Outcomes:** • Shorter median time to discharge in tocilizumab arm than placebo arm (20 vs. 28 days; HR 1.35; 95% CI, 1.02–1.79). • Shorter median ICU LOS in tocilizumab arm than placebo arm (9.8 vs. 15.5 days). • No difference in Day 28 mortality between arms (19.7% in tocilizumab arm vs. 19.4% placebo arm).	**Key Limitations:** • Modest power to detect differences in Day 28 clinical status • More patients in placebo arm than tocilizumab arm received corticosteroids • Few patients on MV **Interpretation:** • There was no difference between arms in Day 28 clinical status or survival. • The median times for recovery and ICU LOS were shorter in the tocilizumab arm than in the placebo arm.

Methods	Results	Limitations and Interpretation
EMPACTA: Double-Blind RCT of Tocilizumab in Hospitalized Patients With COVID-19[5]		

Key Inclusion Criteria:
• PCR-confirmed SARS-CoV-2 infection
• COVID-19 pneumonia
Key Exclusion Criteria:
• 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:
• 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:
	  • 80% on corticosteroids and 53% on RDV in tocilizumab arm
	  • 88% on corticosteroids and 59% on RDV in placebo arm
	Primary Outcome:
	• Proportion of patients who required MV or ECMO or died by Day 28 was 12% in tocilizumab arm and 19% in placebo arm (HR 0.56; 95% CI, 0.33–0.97; *P* = 0.04).
	Secondary Outcomes:
	• Median time to hospital discharge or readiness for discharge was 6.0 days in tocilizumab arm and 7.5 days in placebo arm (HR 1.16; 95% CI, 0.91–1.48).
	• All-cause mortality by Day 28 was not statistically different between arms (10.4% in tocilizumab arm vs. 8.6% in placebo arm).
		Key Limitation:
		• Moderate sample size
		Interpretation:
		• Among patients with COVID-19 pneumonia, tocilizumab lowered rates of MV, ECMO, or death by Day 28 but provided no benefit for 28-day all-cause mortality.

BACC Bay: Double-Blind RCT of Tocilizumab in Hospitalized Patients With COVID-19[6]		

Key Inclusion Criteria:
• Laboratory-confirmed SARS-CoV-2 infection
• ≥2 of the following conditions:
  • Fever >38°C
  • Pulmonary infiltrates
  • Need for oxygen
• ≥1 of the following laboratory criteria:
  • CRP ≥50 mg/L
  • D-dimer >1,000 ng/mL
  • LDH ≥250 U/L
  • Ferritin >500 ng/mL
	Participant Characteristics:
	• Median age 60 years; 58% men; 45% Hispanic/Latinx
	• 50% with BMI ≥30; 49% with HTN; 31% with DM
	• 80% receiving oxygen ≤6 L/min; 4% receiving high-flow oxygen; 16% receiving no supplemental oxygen
	• Concomitant medications:
	  • 11% on corticosteroids and 33% on RDV in tocilizumab arm
	  • 6% on glucocorticoids and 29% on RDV in placebo arm
	Primary Outcome:
	• No difference between arms in rate of Day 28 MV or death (10.6% in tocilizumab arm vs. 12.5% in placebo arm; HR 0.83; 95% CI, 0.38–1.81; P = 0.64).
		Key Limitations:
		• Wide confidence intervals due to small sample size and low event rates
		• Few patients received RDV or corticosteroids
		Interpretation:
		• There was no benefit of tocilizumab in preventing 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
BACC Bay: Double-Blind RCT of Tocilizumab in Hospitalized Patients With COVID-19[6], continued		
Key Exclusion Criteria: • Requiring supplemental oxygen at rate >10 L/min • Recent use of biologic agents or small molecule immunosuppressive therapy that investigators believe place the patient at a higher risk for infection **Interventions:** • Tocilizumab 8 mg/kg plus usual care (n = 161) • Placebo plus usual care (n = 81) **Primary Endpoint:** • 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	**Secondary Outcomes:** • No difference between arms in proportion of patients who had worsening of disease by Day 28 (19% in tocilizumab arm vs. 17% in placebo arm; HR 1.11; 95% CI, 0.59–2.10). • Median number of days to discontinuation of oxygen was 5.0 in tocilizumab arm and 4.9 in placebo arm (*P* = 0.69).	
Double-Blind, RCT of Sarilumab in Hospitalized Patients With Severe or Critical COVID-19[7]		
Key Inclusion Criteria: • Severe or critical laboratory-confirmed COVID-19 • COVID-19 pneumonia **Key Exclusion Criteria:** • Low probability of surviving or remaining at study site • Dysfunction of ≥2 organ systems and need for ECMO or renal replacement therapy **Interventions:** • Sarilumab 400 mg IV (n = 173) • Sarilumab 200 mg IV (n = 159) • Placebo (n = 84) **Primary Endpoint:** • Time to clinical improvement of ≥2 points on a 7-point scale	**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 **Primary Outcome:** • No difference in median time to clinical improvement among the sarilumab arms (10 days for each) and placebo arm (12 days). **Secondary Outcome:** • No difference among the arms in survival rate at Day 29 (92% in placebo arm vs. 90% in sarilumab 200 mg arm vs. 92% in sarilumab 400 mg arm).	**Key Limitations:** • Only 20% of patients received corticosteroids • Moderate sample size and a small placebo arm **Interpretation:** • There was no benefit of sarilumab in hospitalized adults with COVID-19 in time to clinical improvement or mortality. This could be due to the low rate of concomitant corticosteroid use among the study participants.

Methods	Results	Limitations and Interpretation
Double-Blind, RCT of Sarilumab in Hospitalized Patients With Severe or Critical COVID-19[7], continued		
Key Secondary Endpoint: • Survival at Day 29		
REMDACTA: Double-Blind RCT of Tocilizumab and Remdesivir in Hospitalized Patients With Severe COVID-19 Pneumonia[8]		

Key Inclusion Criteria:
• 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
• Infection other than SARS-CoV-2
• 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:
	  • 78% in tocilizumab arm and 83% in placebo arm on NIV or high-flow oxygen
	  • 15% in tocilizumab arm and 11% in placebo arm required MV or ECMO
	• Corticosteroid use:
	  • 83% in tocilizumab arm and 86% in placebo arm at baseline
	  • 88% in each arm during the trial
	Primary Outcome:
	• No difference between arms in 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:
	• There was no difference between the arms in key secondary outcomes:
	  • Proportion of patients in each arm who required MV or died by Day 28 was 29%; time to death was non-evaluable (HR 0.98; 95% CI, 0.72–1.34; $P = 0.90$).
	  • Mean ordinal score for clinical status at Day 14 was 2.8 in tocilizumab arm and 2.9 in placebo arm ($P = 0.72$).
	  • 18% of patients in tocilizumab arm and 20% in placebo arm died by Day 28; time to death was non-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" to 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

References

1. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. 2021;397(10285):1637-1645. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33933206.
2. REMAP-CAP Investigators, Gordon AC, Mouncey PR, et al. Interleukin-6 receptor antagonists in critically ill patients with COVID-19. *N Engl J Med*. 2021;384(16):1491-1502. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33631065.
3. The REMAP-CAP Investigators, Derde LPG. Effectiveness of tocilizumab, sarilumab, and anakinra for critically ill patients with COVID-19: the REMAP-CAP COVID-19 immune modulation therapy domain randomized clinical trial. *medRxiv*. 2021;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.06.18.21259133v2.
4. Rosas IO, Brau N, Waters M, et al. Tocilizumab in hospitalized patients with severe COVID-19 pneumonia. *N Engl J Med*. 2021;384(16):1503-1516. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33631066.
5. Salama C, Han J, Yau L, et al. Tocilizumab in patients hospitalized with COVID-19 pneumonia. *N Engl J Med*. 2021;384(1):20-30. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33332779.
6. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of tocilizumab in patients hospitalized with COVID-19. *N Engl J Med*. 2020;383(24):2333-2344. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33085857.
7. Lescure FX, Honda H, Fowler RA, et al. Sarilumab in patients admitted to hospital with severe or critical COVID-19: a randomised, double-blind, placebo-controlled, Phase 3 trial. *Lancet Respir Med*. 2021;9(5):522-532. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33676590.
8. Rosas IO, Diaz G, Gottlieb RL, et al. Tocilizumab and remdesivir in hospitalized patients with severe COVID-19 pneumonia: a randomized clinical trial. *Intensive Care Med*. 2021;47(11):1258-1270. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34609549.

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

Last Updated: December 16, 2021

Janus Kinase Inhibitors

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

Immunosuppression induced by JAK inhibitors could potentially reduce the inflammation and associated immunopathologies observed in patients with COVID-19. Additionally, JAK inhibitors, particularly baricitinib, have theoretical direct antiviral activity through interference with viral endocytosis, potentially preventing SARS-CoV-2 from entering and infecting susceptible cells.[4]

Recommendations

- See Therapeutic Management of Hospitalized Adults With COVID-19 for the COVID-19 Treatment Guidelines Panel's (the Panel) recommendations on the use of baricitinib and tofacitinib for certain hospitalized patients who require oxygen supplementation.
- The Panel **recommends against** the use of **JAK inhibitors other than baricitinib or tofacitinib** for the treatment of COVID-19, except in a clinical trial **(AIII)**.

Rationale

The Panel's recommendations are based on data from the ACTT-2,[5] COV-BARRIER,[6] and STOP-COVID[7] clinical trials. The ACTT-2 trial demonstrated that baricitinib improved time to recovery when given in combination with remdesivir to hospitalized patients with COVID-19 who require supplemental oxygen but not mechanical ventilation. However, a key limitation of the ACTT-2 trial is that corticosteroids were not used as the standard of care; thus, it was not possible to evaluate the effect of baricitinib when given in addition to corticosteroids.

The COV-BARRIER trial enrolled patients with COVID-19 pneumonia and at least 1 elevated inflammatory marker at enrollment who were not on mechanical ventilation. This trial reported an additional survival benefit of baricitinib when added to the standard of care of corticosteroids (with or without remdesivir). If baricitinib is not available, tofacitinib may be an alternative because it has demonstrated clinical benefit in the STOP-COVID trial.

The clinical trial data on the use of baricitinib and tofacitinib in patients with COVID-19 is summarized below, and all related treatment recommendations are reviewed in Therapeutic Management of Hospitalized Adults With COVID-19.

Monitoring, Adverse Effects, and Drug-Drug Interactions

Most of the data on adverse effects of JAK inhibitors were reported based on chronic use of the agents for the treatment of autoimmune diseases. Adverse effects include infections (typically respiratory and urinary tract infections) and the reactivation of herpes viruses; myelosuppression; transaminase elevations; and, rarely, gastrointestinal perforation. The Food and Drug Administration (FDA) review of a large, randomized, safety clinical trial comparing tofacitinib to antitumor necrosis factor inhibitors in people with rheumatoid arthritis found that tofacitinib was associated with additional serious adverse

events, including heart attack or stroke, cancer, blood clots, and death.[8] The FDA is therefore requiring new and updated warnings for drugs in the JAK inhibitor class, including tofacitinib and baricitinib. Data from randomized trials evaluating the safety of short-term use of JAK inhibitors in patients with COVID-19 are limited. The data to date have not revealed significant safety signals, including thrombosis; however, these trials may be underpowered for detecting rare adverse events.[5-7]

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

Tofacitinib is a cytochrome P 450 (CYP) 3A4 substrate. Dose modifications are required when the drug is administered with strong CYP3A4 inhibitors or when used with a moderate CYP3A4 inhibitor that is coadministered with a strong CYP2C19 inhibitor. Coadministration with a strong CYP3A4 inducer **is not recommended**.

The ACTT-2 and COV-BARRIER trials evaluated oral baricitinib 4 mg once daily, which is twice the standard baricitinib dose (2 mg once daily) for FDA-approved indications.[5,6] In patients with severe hepatic impairment, baricitinib should only be used if the potential benefit outweighs the potential risk.[9] Baricitinib has not been evaluated in clinical studies for FDA-approved indications in patients with an estimated glomerular filtration rate (eGFR) ≤30 mL/min. When baricitinib is used for the treatment of COVID-19 in adults with renal insufficiency, the Panel recommends reducing the dose of baricitinib from 4 mg to 2 mg daily for adults with an eGFR ≥30 to <60 mL/min and to 1 mg daily for those with an eGFR of 15 to <30 mL/min. Baricitinib **is not recommended** for patients with an eGFR <15 mL/min.[9] There are limited clinical data on the use of baricitinib in combination with strong organic anion transporter 3 inhibitors, and, in general, coadministration is not advised.[10,11]

Considerations in Pregnancy

There is a paucity of data on the use of JAK inhibitors in pregnancy. As small molecule-drugs, JAK inhibitors are likely to pass through the placenta, and therefore fetal risk cannot be ruled out.[12] Decisions regarding the administration of JAK inhibitors must include shared decision-making between the pregnant individual and their health care provider, considering potential maternal benefit and fetal risks. Factors that may weigh into the decision-making process include maternal COVID-19 severity, comorbidities, and gestational age. Pregnancy registries provide some outcome data on tofacitinib use during pregnancy for other conditions (e.g., ulcerative colitis, rheumatoid arthritis, psoriasis). Among the 33 cases reported, pregnancy outcomes were similar to those among the general population.[13-15]

Considerations in Children

An FDA Emergency Use Authorization (EUA) has been issued for the use of baricitinib in hospitalized adults and children aged ≥2 years with COVID-19 who require supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).[9] The safety and efficacy of baricitinib have not been evaluated in pediatric patients with COVID-19. As noted above, tofacitinib was shown to decrease the risk of respiratory failure and death in adults with COVID-19 in the STOP-COVID trial.[7] Tofacitinib is FDA approved for a pediatric indication; however, the safety and efficacy of tofacitinib have not been evaluated in pediatric patients with COVID-19. Thus, there is insufficient evidence to recommend either for or against the use of baricitinib in combination with corticosteroids and/or remdesivir for the treatment of COVID-19 in hospitalized children.

Baricitinib

Baricitinib is an oral JAK inhibitor that is selective for JAK1 and JAK2 and is FDA approved for the

treatment of rheumatoid arthritis.[10] Baricitinib can modulate downstream inflammatory responses via JAK1/JAK2 inhibition and has exhibited dose-dependent inhibition of IL-6-induced STAT3 phosphorylation.[16] Baricitinib has postulated antiviral effects by blocking SARS-CoV-2 from entering and infecting lung cells.[17] Baricitinib reduced inflammation and lung pathology in macaques infected with SARS-CoV-2, but an antiviral effect was not confirmed.[18]

Clinical Data for COVID-19

In the ACTT-2 trial, 1,033 patients hospitalized with COVID-19 were randomized 1:1 to receive baricitinib 4 mg daily for 14 days (or until hospital discharge) or placebo, both given in combination with remdesivir. The primary endpoint was time to recovery as measured on an 8-category ordinal scale. Recovery time was shorter in the baricitinib arm (7 days) than in the placebo arm (8 days) (rate ratio for recovery 1.16; 95% CI, 1.01–1.32; $P = 0.03$). Mortality by 28 days was lower in the baricitinib arm than in the placebo arm, but the difference was not statistically significant. A key limitation of the study is that corticosteroids were not used as background standard care for patients with severe or critical COVID-19 pneumonia.[5]

In the COV-BARRIER trial, 1,525 hospitalized patients with COVID-19 pneumonia and an elevation in 1 or more inflammatory markers were randomized 1:1 to receive baricitinib 4 mg orally or placebo for up to 14 days (or until hospital discharge). Patients on mechanical ventilation were excluded from study enrollment. Overall, 79% of patients received corticosteroids and 19% received remdesivir. The primary endpoint was the proportion of patients who progressed to high-flow oxygen, noninvasive ventilation, mechanical ventilation, or death by Day 28. Progression to the primary endpoint occurred among 27.8% of patients in the baricitinib arm versus 30.5% in the placebo arm (OR 0.85; 95% CI, 0.67–1.08; $P = 0.18$). All-cause mortality within 28 days, which was a key secondary endpoint, was 8.1% in the baricitinib arm and 13.1% in the placebo arm, resulting in a 38.2% reduction in mortality associated with baricitinib (HR 0.57; 95% CI, 0.41–0.78). The mortality difference was most pronounced in the subgroup of patients receiving high-flow oxygen or noninvasive ventilation at baseline (17.5% for baricitinib recipients vs. 29.4% for placebo recipients; HR 0.52; 95% CI, 0.33–0.80). However, subgroup analyses did not identify a statistically significant benefit of baricitinib versus placebo among patients receiving low-flow oxygen at baseline. The occurrence of adverse events, serious adverse events, serious infections, and venous thromboembolic events was comparable in the baricitinib and placebo arms.[6]

The COV-BARRIER trial added a critically ill cohort to the original study. In this cohort, participants on mechanical ventilation or ECMO at baseline (n = 101) were randomly assigned to baricitinib 4 mg (n = 51) or placebo (n = 50) for up to 14 days in combination with the standard of care. At baseline, 86% of participants were receiving corticosteroids and 2% were receiving remdesivir. Baricitinib significantly reduced the prespecified endpoint of 28-day all-cause mortality when compared with placebo (39.2% vs. 58.0%; HR 0.54; 95% CI, 0.31–0.96; $P = 0.03$). Significant reductions were also reported with baricitinib versus placebo in 60-day mortality (45% vs. 62%; $P = 0.027$) and hospital days (23.7 vs. 26.1 days; $P = 0.05$). The implications of these findings are limited due to the very small sample size of this addendum trial population.[19]

The collective data from these studies have informed the Panel's recommendations on the use of baricitinib in hospitalized patients with COVID-19. The specific recommendations and additional information on the rationale can be found in Therapeutic Management of Hospitalized Adults With COVID-19.

Clinical Trials

Please see ClinicalTrials.gov for the latest information on studies of baricitinib for the treatment of COVID-19.

Drug Availability

Baricitinib is approved by the FDA for the treatment of rheumatoid arthritis. On November 19, 2020, the FDA issued an initial EUA for the use of baricitinib in combination with remdesivir for the treatment of COVID-19 in certain hospitalized children and adults who require supplemental oxygen, mechanical ventilation, or ECMO. The EUA was revised on July 28, 2021, to remove the requirement that baricitinib be used only in combination with remdesivir for the treatment of COVID-19.[9]

Tofacitinib

Tofacitinib is the prototypical JAK inhibitor, predominantly selective for JAK1 and JAK3, with modest activity against JAK2, and, as such, can block signaling from gamma-chain cytokines (e.g., IL-2, IL-4) and glycoprotein 130 proteins (e.g., IL-6, IL-11, interferons). It is an oral agent first approved by the FDA for the treatment of rheumatoid arthritis and has been shown to decrease levels of IL-6 in patients with this disease.[20] Tofacitinib is also FDA approved for the treatment of psoriatic arthritis, juvenile idiopathic arthritis, and ulcerative colitis.[21]

Clinical Data for COVID-19

The double-blind STOP-COVID trial randomized 289 hospitalized patients with COVID-19 in Brazil to receive tofacitinib 10 mg or placebo orally twice daily for up to 14 days (or until hospital discharge). Patients who were on mechanical ventilation or who had an immunocompromising condition were excluded from the trial. The background standard of care included corticosteroids (79.2% of patients were receiving corticosteroids at randomization and overall, 89.3% received corticosteroids during the study) but not remdesivir. The primary outcome of death or respiratory failure through Day 28 occurred in 18.1% of patients in the tofacitinib arm and 29.0% in the placebo arm (risk ratio 0.63; 95% CI, 0.41–0.97). All-cause mortality within 28 days was 2.8% in the tofacitinib arm and 5.5% in the placebo arm (risk ratio 0.49; 95% CI, 0.15–1.63). Serious adverse events occurred in 14.2% of the patients in the tofacitinib arm and 12.0% in the placebo arm. Limitations of the trial include the small sample size.[7]

Clinical Trials

Please see ClinicalTrials.gov for the latest information on studies of tofacitinib for the treatment of COVID-19.

Ruxolitinib

Ruxolitinib is an oral JAK inhibitor selective for JAK1 and JAK2 that is currently approved for myelofibrosis, polycythemia vera, and acute graft-versus-host disease.[22] Like baricitinib, it can modulate downstream inflammatory responses via JAK1/JAK2 inhibition and has exhibited dose-dependent inhibition of IL-6-induced STAT3 phosphorylation.[16] Ruxolitinib also has postulated antiviral effects by blocking SARS-CoV-2 from entering and infecting lung cells.[17]

Clinical Data for COVID-19

A small, single-blind, Phase 2 randomized controlled trial in patients with COVID-19 in China compared ruxolitinib 5 mg orally twice daily (n = 20) with placebo (administered as vitamin C 100 mg; n = 21), both given in combination with standard of care. Treatment with ruxolitinib was associated with a nonsignificant reduction in the median time to clinical improvement (12 days for ruxolitinib recipients vs. 15 days for placebo recipients; $P = 0.15$), defined as a 2-point improvement on a 7-category ordinal scale or as hospital discharge. There was no difference between the arms in the median time to discharge (17 days for ruxolitinib arm vs. 16 days for placebo arm; $P = 0.94$). Limitations of this study include the small sample size.[23] A Phase 3 trial of ruxolitinib in patients with COVID-19-associated acute respiratory distress syndrome is currently in progress (ClinicalTrials.gov Identifier NCT04377620).

Clinical Trials

Please see ClinicalTrials.gov for the latest information on studies of ruxolitinib for the treatment of COVID-19.

Bruton's Tyrosine Kinase Inhibitors

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

Recommendation

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

Acalabrutinib

Acalabrutinib is a second-generation, oral BTK inhibitor that is FDA approved to treat B-cell malignancies (i.e., chronic lymphocytic leukemia/small lymphocytic lymphoma, mantle cell lymphoma). It has a better toxicity profile than first-generation BTK inhibitors (e.g., ibrutinib) because it has less off-target activity for other kinases.[24] Acalabrutinib is proposed for use in patients with COVID-19 because it can modulate signaling that promotes inflammation.

Clinical Data for COVID-19

Data regarding acalabrutinib are limited to the results from a prospective case series of 19 patients with severe COVID-19.[25] Evaluation of the data to discern any clinical benefit is limited by the study's small sample size and lack of a control group.

Clinical Trials

Please see ClinicalTrials.gov for the latest information on studies of acalabrutinib for the treatment of COVID-19.

Ibrutinib

Ibrutinib is a first-generation BTK inhibitor that is FDA approved to treat various B-cell malignancies[26] and to prevent chronic graft-versus-host disease in stem cell transplant recipients.[27] Based on results from a small case series, ibrutinib has been theorized to reduce inflammation and protect against ensuing lung injury in patients with COVID-19.[28]

Clinical Data for COVID-19

Data regarding ibrutinib are limited to those from an uncontrolled, retrospective case series of 6 patients with COVID-19 who were receiving the drug for a condition other than COVID-19.[28] Evaluation of the data for any clinical benefit is limited by the series' small sample size and lack of a control group.

Clinical Trials

Please see ClinicalTrials.gov for the latest information on studies of ibrutinib for the treatment of COVID-19.

Zanubrutinib

Zanubrutinib is a second-generation, oral BTK inhibitor that is FDA approved to treat mantle cell lymphoma.[29] It has been shown to have fewer toxicities than first-generation BTK inhibitors (e.g., ibrutinib) because of less off-target activity for other kinases.[30] Zanubrutinib is proposed to benefit patients with COVID-19 by modulating signaling that promotes inflammation.

Clinical Data for COVID-19

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

Clinical Trials

Please see ClinicalTrials.gov for the latest information on studies of zanubrutinib for the treatment of COVID-19.

Adverse Effects and Monitoring

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

Considerations in Pregnancy

There is a paucity of data on human pregnancy and BTK inhibitor use. In animal studies, acalabrutinib and ibrutinib in doses exceeding the therapeutic human dose were associated with interference with embryofetal development.[26,31] Based on these data, use of BTK inhibitors that occurs during organogenesis may be associated with fetal malformations. The impact of use later in pregnancy is unknown. Risks of use should be balanced against potential benefits.

Considerations in Children

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

References

1. Babon JJ, Lucet IS, Murphy JM, Nicola NA, Varghese LN. The molecular regulation of Janus kinase (JAK) activation. *Biochem J*. 2014;462(1):1-13. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25057888.
2. Bousoik E, Montazeri Aliabadi H. "Do we know jack" about JAK? A closer look at JAK/STAT signaling pathway. *Front Oncol*. 2018;8:287. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30109213.
3. Zhang W, Zhao Y, Zhang F, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): the perspectives of clinical immunologists from China. *Clin Immunol.* 2020;214:108393. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32222466.
4. Stebbing J, Phelan A, Griffin I, et al. COVID-19: combining antiviral and anti-inflammatory treatments. *Lancet Infect Dis*. 2020;20(4):400-402. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32113509.
5. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus remdesivir for hospitalized adults with COVID-19. *N Engl J Me*d. 2021;384(9):795-807. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33306283.
6. Marconi VC, Ramanan AV, de Bono S, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled Phase 3 trial. *Lancet Respir Med*. 2021;9(12):1407-1418. Available at: https://pubmed.ncbi.nlm.nih.gov/34480861/.
7. Guimaraes PO, Quirk D, Furtado RH, et al. Tofacitinib in patients hospitalized with COVID-19 pneumonia. *N Engl J Med*. 2021;385(5):406-415. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34133856.
8. Food and Drug Administration. FDA requires warnings about increased risk of serious heart-related events, cancer, blood clots, and death for JAK inhibitors that treat certain chronic inflammatory conditions. 2021. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-warnings-about-increased-risk-serious-heart-related-events-cancer-blood-clots-and-death. Accessed December 2, 2021.
9. Food and Drug Administration. Fact sheet for healthcare providers: Emergency Use Authorization (EUA) of baricitinib. 2021. Available at: https://www.fda.gov/media/143823/download.
10. Baricitinib (Olumiant) [package insert]. Food and Drug Administration. 2019. Available at:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/207924s001lbl.pdf.

11. Posada MM, Cannady EA, Payne CD, et al. Prediction of transporter-mediated drug-drug interactions for baricitinib. *Clin Transl Sci*. 2017;10(6):509-519. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28749581.
12. Sammaritano LR, Bermas BL, Chakravarty EE, et al. 2020 American College of Rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases. *Arthritis Rheumatol*. 2020;72(4):529-556. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32090480.
13. Clowse ME, Feldman SR, Isaacs JD, et al. Pregnancy outcomes in the tofacitinib safety databases for rheumatoid arthritis and psoriasis. *Drug Saf*. 2016;39(8):755-762. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27282428.
14. Mahadevan U, Dubinsky MC, Su C, et al. Outcomes of pregnancies with maternal/paternal exposure in the tofacitinib safety databases for ulcerative colitis. *Inflamm Bowel Dis*. 2018;24(12):2494-2500. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29982686.
15. Wieringa JW, van der Woude CJ. Effect of biologicals and JAK inhibitors during pregnancy on health-related outcomes in children of women with inflammatory bowel disease. *Best Pract Res Clin Gastroenterol*. 2020;44-45:101665. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32359679.
16. McInnes IB, Byers NL, Higgs RE, et al. Comparison of baricitinib, upadacitinib, and tofacitinib mediated regulation of cytokine signaling in human leukocyte subpopulations. *Arthritis Res Ther*. 2019;21(1):183. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31375130.
17. Richardson P, Griffin I, Tucker C, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Lancet*. 2020;395(10223):e30-e31. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32032529.
18. Hoang TN, Pino M, Boddapati AK, et al. Baricitinib treatment resolves lower-airway macrophage inflammation and neutrophil recruitment in SARS-CoV-2-infected rhesus macaques. *Cell*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33278358.
19. Ely EW, Ramanan AV, Kartman CE, et al. Baricitinib plus standard of care for hospitalised adults with COVID-19 on invasive mechanical ventilation or extracorporeal membrane oxygenation: results of a randomised, placebo-controlled trial. *medRxiv*. 2021;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.10.11.21263897v2.
20. Migita K, Izumi Y, Jiuchi Y, et al. Effects of Janus kinase inhibitor tofacitinib on circulating serum amyloid A and interleukin-6 during treatment for rheumatoid arthritis. *Clin Exp Immunol*. 2014;175(2):208-214. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24665995.
21. Tofacitinib (Xeljanz) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/203214s024,208246s010lbl.pdf.
22. Ruxolitinib (JAKAFI) [package insert]. 2020. Available at: https://www.jakafi.com/pdf/prescribing-information.pdf.
23. Cao Y, Wei J, Zou L, et al. Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): A multicenter, single-blind, randomized controlled trial. *J Allergy Clin Immunol*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32470486.
24. Owen C, Berinstein NL, Christofides A, Sehn LH. Review of Bruton tyrosine kinase inhibitors for the treatment of relapsed or refractory mantle cell lymphoma. *Curr Oncol*. 2019;26(2):e233-e240. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31043832.
25. Roschewski M, Lionakis MS, Sharman JP, et al. Inhibition of Bruton tyrosine kinase in patients with severe COVID-19. *Sci Immunol*. 2020;5(48). Available at: https://www.ncbi.nlm.nih.gov/pubmed/32503877.
26. Ibrutinib (Imbruvica) [package insert]. Food and Drug Administration. 2015. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205552s002lbl.pdf.
27. Food and Drug Administration. FDA expands ibrutinib indications to chronic GVHD. 2017. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-expands-ibrutinib-indications-chronic-

gvhd. Accessed December 2, 2021.

28. Treon SP, Castillo JJ, Skarbnik AP, et al. The BTK inhibitor ibrutinib may protect against pulmonary injury in COVID-19-infected patients. *Blood*. 2020;135(21):1912-1915. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32302379.
29. Zanubrutinib (Brukinsa) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213217s000lbl.pdf.
30. Tam C, Grigg AP, Opat S, et al. The BTK inhibitor, Bgb-3111, is safe, tolerable, and highly active in patients with relapsed/refractory B-cell malignancies: initial report of a Phase 1 first-in-human trial. *Blood*. 2015;126(23):832. Available at: https://ashpublications.org/blood/article/126/23/832/136525/The-BTK-Inhibitor-Bgb-3111-Is-Safe-Tolerable-and.
31. Acalabrutinib (Calquence) [package insert]. Food and Drug Administration. 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/210259s000lbl.pdf.

Table 4f. Characteristics of Immunomodulators

Last Updated: December 16, 2021

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

Drug Name	Dosing Regimen *The doses listed are for approved indications or from clinical trials or clinical experience in patients with COVID-19.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Colchicine *Not approved by the FDA and not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*					
Colchicine	**Dose for COVID-19 in COLCORONA Trial:** • Colchicine 0.5 mg twice daily for 3 days and then once daily for 27 days[1]	• Diarrhea • Nausea • Vomiting • Cramping • Abdominal pain • Bloating • Loss of appetite • Neuromyotoxicity (rare)[2] • Blood dyscrasias (rare)	• CBC • Renal function • Hepatic function	• P-gp and CYP3A4 substrate • The risk of myopathy may be increased with the concomitant use of certain HMG-CoA reductase inhibitors (e.g., atorvastatin, lovastatin, simvastatin) due to potential competitive interactions mediated by P-gp and CYP3A4 pathways. • Fatal colchicine toxicity has been reported in individuals with renal or hepatic impairment who used colchicine in conjunction with P-gp inhibitors or strong CYP3A4 inhibitors.	• Use of colchicine **should be avoided** in patients with severe renal insufficiency, and those with moderate renal insufficiency who receive the drug should be monitored for AEs. • A list of clinical trials is available: Colchicine **Availability:** • In the COLCORONA trial, 0.5 mg colchicine tablets were used for dosing; in the United States, colchicine is available as 0.6 mg tablets.

Drug Name	Dosing Regimen *The doses listed are for approved indications or from clinical trials or clinical experience in patients with COVID-19.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Corticosteroids (Inhaled) *Not approved by the FDA and not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*					
Budesonide (Inhaled)	**Dose for COVID-19 in Clinical Trials:** • Budesonide 800 mcg oral inhalation twice daily until symptom resolution or for up to 14 days[3,4]	• Secondary infections • Oral thrush • Systemic AEs (less common)	• Signs of AEs involving the oral mucosa or throat including thrush • Signs of systemic corticosteroid effects (e.g., adrenal suppression)	• CYP3A4 substrate • **Do not use** with strong CYP3A4 inhibitors.	• A list of clinical trials is available: Inhaled Budesonide
Ciclesonide (Inhaled)	**Dose for COVID-19 in Clinical Trials:** • Ciclesonide 160 mcg: 2 MDI inhalations twice daily for 30 days[5]	• Secondary infections • Oral thrush • Systemic AEs (less common)	• Signs of AEs involving the oral mucosa or throat including thrush • Signs of systemic corticosteroid effects (e.g., adrenal suppression)	• CYP3A4 substrate • Effect of strong CYP3A4 inhibitors on ciclesonide exposure is not expected to be as significant as that on budesonide.	• A list of clinical trials is available: Ciclesonide
Corticosteroid (Systemic) *Recommended by the Panel for the treatment of COVID-19 in certain nonhospitalized and 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[6]
		• Hyperglycemia
		• Secondary infections
		• Reactivation of latent infections (e.g., HBV, HSV, strongyloidiasis, TB)
		• Psychiatric disturbances
		• Avascular necrosis
		• Adrenal insufficiency
		• Increased BP
		• Peripheral edema
		• Myopathy (particularly if used with neuromuscular blocking agents)
			• Blood glucose
			• BP
			• Signs and symptoms of new infection
			• Cases of disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with corticosteroids and tocilizumab. Prophylactic treatment for strongyloidiasis (e.g., with IVM) should be considered for persons from areas where *Strongyloides* is endemic.[7]
				• Moderate CYP3A4 inducer
				• CYP3A4 substrate
				• Although coadministration of RDV and DEX has not been formally studied, a clinically significant PK interaction is not predicted (Gilead, written communication, August 2020).
					• If DEX is not available, an alternative corticosteroid (e.g., prednisone, methylprednisolone, hydrocortisone) can be used.
					• The approximate total daily dose equivalencies for these glucocorticoids to DEX 6 mg (PO or IV) are:
					  • Prednisone 40 mg
					  • Methylprednisolone 32 mg
					  • Hydrocortisone 160 mg
					• A list of clinical trials is available: Dexamethasone

Drug Name	Dosing Regimen *The doses listed are for approved indications or from clinical trials or clinical experience in patients with COVID-19.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Fluvoxamine *Not approved by the FDA and not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*					
Fluvoxamine	**Dose for COVID-19 in Clinical Trials:** • Various dosing regimens used, including: • Fluvoxamine 50 mg twice daily • Fluvoxamine 100 mg twice daily • Fluvoxamine 100 mg 3 times daily	• Nausea • Diarrhea • Dyspepsia • Asthenia • Insomnia • Somnolence • Sweating • Suicidal ideation (rare)	• Hepatic function • Drug interactions • Monitor for withdrawal symptoms when tapering dose	• CYP2D6 substrate • Fluvoxamine inhibits several CYP isoenzymes (CYP1A2, CYP2C9, CYP3A4, CYP2C19, CYP2D6) • Coadministration of tizanidine, thioridazine, alosetron, or pimozide with fluvoxamine is **contraindicated**.	• Fluvoxamine may enhance anticoagulant effects of antiplatelets and anticoagulants; consider additional monitoring when these drugs are used concomitantly with fluvoxamine. • The use of MAOIs concomitantly with fluvoxamine or within 14 days of treatment with fluvoxamine is **contraindicated**. • A list of clinical trials is available: Fluvoxamine

Drug Name	Dosing Regimen *The doses listed are for approved indications or from clinical trials or clinical experience in patients with COVID-19.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Interleukin-1 Inhibitors *Not approved by the FDA and not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*					
Anakinra	**FDA-Approved Dose for Rheumatoid Arthritis:** • Anakinra 100 mg SQ once daily **Dose for COVID-19 in Clinical Trials:** • Dose and duration vary by study. • Has also been used as IV infusion.	• Neutropenia (particularly when used concomitantly with other agents that can cause neutropenia) • Anaphylaxis and angioedema • Headache • Nausea • Diarrhea • Sinusitis • Arthralgia • Flu-like symptoms • Abdominal pain • Injection site reactions • Liver enzyme elevations	• CBC with differential • Liver enzymes • Renal function; reduce dose if CrCl <30 mL/min.	• Use with TNF-blocking agents **is not recommended** due to increased risk of infection. • **Avoid** concomitant administration of live vaccines.	• Anakinra for IV administration is not an approved formulation in the United States.[8] • A list of clinical trials is available: Anakinra

Drug Name	Dosing Regimen *The doses listed are for approved indications or from clinical trials or clinical experience in patients with COVID-19.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Interleukin-1 Inhibitors, continued					

Canakinumab	**FDA-Approved Dose for Systemic Juvenile Idiopathic Arthritis:**
	• Canakinumab 4 mg/kg (maximum 300 mg) SQ every 4 weeks[9]
	Dose for COVID-19 in Clinical Trials:
	• Dose and duration vary by study.
	CAN-COVID Trial:
	• Single weight-based dose of canakinumab in 250 mL of 5% dextrose by IV infusion over 2 hours:[10]
	  • 40 to <60 kg: 450 mg
	  • 60–80 kg: 600 mg
	  • >80 kg: 750 mg
		• HSR
		• Neutropenia
		• Nasopharyngitis
		• Diarrhea
		• Respiratory tract infections
		• Bronchitis
		• Gastroenteritis
		• Pharyngitis
		• Musculoskeletal pain
		• Vertigo
		• Abdominal pain
		• Injection site reactions
		• Liver enzyme elevations
			• HSR
			• CBC with differential
			• Liver enzymes
				• Binding of canakinumab to IL-1 may increase formation of CYP enzymes and alter metabolism of drugs that are CYP substrates.
				• Use with TNF-blocking agents **is not recommended** due to potential increased risk of infection.
				• **Avoid** concomitant administration of live vaccines.
					• Canakinumab for IV administration is not an approved formulation in the United States.[9]
					• A list of clinical trials is available: Canakinumab

Drug Name	Dosing Regimen *The doses listed are for approved indications or from clinical trials or clinical experience in patients with COVID-19.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Interleukin-6 Inhibitors					
Anti-Interleukin-6 Receptor Monoclonal Antibodies *Recommended by the Panel for the treatment of COVID-19 in certain nonhospitalized and hospitalized patients.*					
Sarilumab[11]	**Dose for COVID-19 in Clinical Trials:** • Single dose of sarilumab 400 mg IV[12] • The IV formulation of sarilumab is not approved by the FDA, but in a clinical trial, a single SQ dose (using the prefilled syringe, not the prefilled pen) of sarilumab 400 mg was reconstituted in 100 cc 0.9% NaCl and given as an IV infusion over a 1-hour period. • Sarilumab infusion should be used within 4 hours of preparation; it can be stored at room temperature until administered.	• Neutropenia, thrombocytopenia • GI perforation • HSR • Increased liver enzymes • HBV reactivation • Infusion-related reaction	• HSR • Infusion reactions • Neutrophils • Platelets • Liver enzymes	• Elevated IL-6 may downregulate CYP enzymes; thus, use of sarilumab may lead to increased metabolism of drugs that are CYP substrates. • The effects of sarilumab on CYP enzymes may persist for weeks after the drug is stopped.	• Treatment with sarilumab may mask signs of acute inflammation or infection by suppressing fever and CRP levels. • A list of clinical trials is available: Sarilumab **Availability:** • Sarilumab for IV administration is not an approved formulation in the United States.
Tocilizumab[13]	**EUA Dose for COVID-19** *For Hospitalized Patients Aged ≥2 Years Based on Body Weight:* • <30 kg: Tocilizumab 12 mg/kg administered by IV infusion over 1 hour • ≥30 kg: Tocilizumab 8 mg/kg (maximum dose 800 mg) administered by IV infusion over 1 hour	• Infusion-related reaction • HSR • GI perforation • Hepatotoxicity • Treatment-related changes on laboratory tests for neutrophils, platelets, lipids, and liver enzymes • HBV reactivation	• HSR • Infusion reactions • Neutrophils • Platelets • Liver enzymes • Cases of disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with tocilizumab and corticosteroids.	• Elevated IL-6 may downregulate CYP enzymes; use of tocilizumab may lead to increased metabolism of drugs that are CYP substrates. • The effects of tocilizumab on CYP enzymes may persist for weeks after the drug is stopped.	• Tocilizumab use **should be avoided** in patients who are significantly immunocompromised. The safety of using tocilizumab plus a corticosteroid in immunocompromised patients is unknown. • The SQ formulation of tocilizumab **is not intended** for IV administration. • A list of clinical trials is available: Tocilizumab

Drug Name	Dosing Regimen *The doses listed are for approved indications or from clinical trials or clinical experience in patients with COVID-19.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Interleukin-6 Inhibitors, continued					
Anti-Interleukin-6 Receptor Monoclonal Antibodies, continued					
Tocilizumab[13], continued	• Per the EUA, if clinical signs or symptoms worsen or do not improve following the first infusion, 1 additional dose of tocilizumab may be administered at least 8 hours after the first dose.	• Secondary infections	Prophylactic treatment for strongyloidiasis (e.g., with IVM) should be considered for persons from areas where *Strongyloides* is endemic.[7]		**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 tocilizumab for SQ administration for the treatment of COVID-19.[14]
Anti-Interleukin-6 Monoclonal Antibody *Not approved by the FDA and not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*					
Siltuximab	**FDA-Approved Dose for Multicentric Castleman Disease:** • Siltuximab 11 mg/kg administered over 1 hour by IV infusion every 3 weeks[15] **Dose for COVID-19:** • Dose and duration unknown	• Infusion-related reaction • HSR • GI perforation • Neutropenia • HTN • Dizziness • Rash • Pruritus • Hyperuricemia	• Neutrophils • HSR • Infusion reactions	• Elevated IL-6 may downregulate CYP enzymes; use of siltuximab may lead to increased metabolism of drugs that are CYP substrates. • The effects of siltuximab on CYP enzymes may persist for weeks after therapy is stopped.	• Treatment with siltuximab may mask signs of acute inflammation or infection by suppressing fever and CRP levels. • A list of clinical trials is available: Siltuximab

Drug Name	Dosing Regimen *The doses listed are for approved indications or from clinical trials or clinical experience in patients with COVID-19.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Kinase Inhibitors					
Janus Kinase Inhibitors *Baricitinib and Tofacitinib: Recommended by the Panel for the treatment of COVID-19 in certain nonhospitalized and hospitalized patients.* *Ruxolitinib: Not approved by the FDA and not recommended by the Panel for the treatment of COVID-19. Currently under investigation in clinical trials.*					
Baricitinib[16]	**EUA Dose for COVID-19**[17] *For Adults and Children Aged ≥9 Years Based on eGFR:* • ≥60 mL/min/1.73 m^2: Baricitinib 4 mg PO once daily • 30 to <60 mL/min/1.73 m^2: Baricitinib 2 mg PO once daily • 15 to <30 mL/min/1.73 m^2: Baricitinib 1 mg PO once daily • eGFR <15 mL/min/1.73 m^2: **Not recommended** *For Children Aged 2 to <9 Years Based on eGFR:* • ≥60 mL/min/1.73 m^2: Baricitinib 2 mg PO once daily • 30 to <60 mL/min/1.73 m^2: Baricitinib 1 mg PO once daily • <30 mL/min/1.73 m^2: **Not recommended** **Duration of Therapy:** • For up to 14 days or until hospital discharge	• Lymphoma and other malignancies • Thrombosis • GI perforation • Treatment-related changes in lymphocytes, neutrophils, Hgb, liver enzymes • HSV reactivation • Herpes zoster • Serious cardiac-related events (e.g., MI, stroke)	• CBC with differential • Renal function • Liver enzymes • New infections	• Dose modification is recommended when administering concurrently with a strong OAT3 inhibitor. • **Avoid** concomitant administration of live vaccines.	• Baricitinib for the treatment of COVID-19 is available through an FDA EUA. See the EUA for dosing guidance for patients with: • ALC <200 cells/μL • ANC <500 cells/μL • If increases in ALT or AST are observed and DILI is suspected, interrupt baricitinib treatment until the diagnosis of DILI is excluded. • A list of clinical trials is available: Baricitinib **Availability:** • Baricitinib, which has been approved for non-COVID-19 indications, is available commercially and through an EUA for the treatment of hospitalized patients with COVID-19 aged ≥2 years.[17]

Drug Name	Dosing Regimen *The doses listed are for approved indications or from clinical trials or clinical experience in patients with COVID-19.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Kinase Inhibitors, continued					
Janus Kinase Inhibitors, continued					
Ruxolitinib	**Dose for FDA-Approved Indications:** • Ruxolitinib 5 mg–20 mg PO twice daily **Dose for COVID-19 in Clinical Trials:** • Ruxolitinib 5 mg–20 mg PO twice daily for 14 days[18]	• Thrombocytopenia • Anemia • Neutropenia • Liver enzyme elevations • Risk of infection • Dizziness • Headache • Diarrhea • CPK elevation • Herpes zoster	• CBC with differential • Liver enzymes • New infections	• Dose modification required when administered with strong CYP3A4 inhibitor. • **Avoid** use with fluconazole doses >200 mg.	• Dose modification may be required in patients with hepatic impairment, moderate or severe renal impairment, or thrombocytopenia. • A list of clinical trials is available: Ruxolitinib
Tofacitinib	**Dose for COVID-19 in Clinical Trial:** • Tofacitinib 10 mg PO twice daily for up to 14 days or until hospital discharge[19]	• Thrombotic events (e.g., PE, DVT, arterial thrombosis) • Anemia • Risk of infection • GI perforation • Diarrhea • Headache • Herpes zoster • Lipid elevations • Liver enzyme elevations • Lymphoma and other malignancies • Serious cardiac-related events (e.g., MI, stroke)	• CBC with differential • Liver enzymes • New infections	• Dose modifications required when administered with strong CYP3A4 inhibitors or when used with a moderate CYP3A4 inhibitor that is coadministered with a strong CYP2C19 inhibitor. • Coadministration with strong CYP3A4 inducers **is not recommended**. • **Avoid** concomitant administration of live vaccines.	• **Avoid** use in patients with ALC <500 cells/mm^3, ANC <1,000 cells/mm^3, or Hgb <9 grams/dL. • Dose modification may be required in patients with moderate or severe renal impairment or moderate hepatic impairment. • A list of clinical trials is available: Tofacitinib

Drug Name	Dosing Regimen *The doses listed are for approved indications or from clinical trials or clinical experience in patients with COVID-19.*	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Non-SARS-CoV-2 Specific Immunoglobulin *Primarily used for the treatment of multi-system inflammatory syndrome in children (MIS-C). Currently under investigation in clinical trials.*					
Non-SARS-CoV-2 Specific Immunoglobulin	• Dose varies based on indication and formulation.	• Allergic reactions, including anaphylaxis • Renal failure • Thrombotic events • Aseptic meningitis syndrome • Hemolysis • TRALI • Transmission of infectious pathogens • AEs may vary by formulation. • AEs may be increased with high dose, rapid infusion, or in patients with underlying conditions.	• Transfusion-related reactions • Vital signs at baseline and during and after infusion • Renal function; discontinue treatment if function deteriorates.	• IVIG may interfere with immune response to certain vaccines.	• A list of clinical trials is available: Intravenous Immunoglobulin

Key: AE = adverse event; ALC = absolute lymphocyte count; ALT = alanine transaminase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BP = blood pressure; CBC = complete blood count; CPK = creatine phosphokinase; CrCl = creatinine clearance; CRP = C-reactive protein; CYP = cytochrome P450; DEX = dexamethasone; DILI = drug-induced liver injury; DVT = deep vein thrombosis; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; GI = gastrointestinal; HBV = hepatitis B; Hgb = hemoglobin; HSR = hypersensitivity reaction; HSV = herpes simplex virus; HTN = hypertension; IL = interleukin; IV = intravenous; IVIG = intravenous immunoglobulin; IVM = ivermectin; MAOI = monoamine oxidase inhibitor; MDI = metered dose inhaler; MI= myocardial infarction; MV = mechanical ventilation; NaCl = sodium chloride; NIV = noninvasive ventilation; OAT = organic anion transporter; the Panel = the COVID-19 Treatment Guidelines Panel; PE = pulmonary embolism; P-gp= P-glycoprotein; PK = pharmacokinetic; PO = orally; RDV = remdesivir; SQ = subcutaneous; TB = tuberculosis; TNF = tumor necrosis factor; TRALI = transfusion-related acute lung injury

References

1. Tardif JC, Bouabdallaoui N, L'Allier PL, et al. Colchicine for community-treated patients with COVID-19 (COLCORONA): a Phase 3, randomised, double-blinded, adaptive, placebo-controlled, multicentre trial. *Lancet Respir Med*. 2021;9(8):924-932. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34051877.

2. Colchicine (Colcrys) [package insert]. Food and Drug Administration. 2012. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022352s017lbl.pdf.
3. Ramakrishnan S, Nicolau DV, Jr., Langford B, et al. Inhaled budesonide in the treatment of early COVID-19 (STOIC): a Phase 2, open-label, randomised controlled trial. *Lancet Respir Med*. 2021;9(7):763-772. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33844996.
4. Yu LM, Bafadhel M, Dorward J, et al. Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. *Lancet*. 2021 Sep 4;398(10303):843-855. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34388395.
5. Clemency BM, Varughese R, Gonzalez-Rojas Y, et al. Efficacy of inhaled ciclesonide for outpatient treatment of adolescents and adults With symptomatic COVID-19: a randomized clinical trial. *JAMA Intern Med*. 2021;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34807241.
6. Randomised Evaluation of COVID-19 Therapy (RECOVERY). Low-cost dexamethasone reduces death by up to one third in hospitalised patients with severe respiratory complications of COVID-19. 2020. Available at: https://www.recoverytrial.net/news/low-cost-dexamethasone-reduces-death-by-up-to-one-third-in-hospitalised-patients-with-severe-respiratory-complications-of-covid-19. Accessed February 9, 2021.
7. Stauffer WM, Alpern JD, Walker PF. COVID-19 and dexamethasone: a potential strategy to avoid steroid-related strongyloides hyperinfection. *JAMA*. 2020;324(7):623-624. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32761166.
8. Anakinra (Kineret) [package insert]. Food and Drug Administration. 2012. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103950s5136lbl.pdf.
9. Canakinumab (Ilaris) [package insert]. Food and Drug Administration. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125319s100lbl.pdf.
10. Caricchio R, Abbate A, Gordeev I, et al. Effect of canakinumab vs placebo on survival without invasive mechanical ventilation in patients hospitalized with severe COVID-19: a randomized clinical trial. *JAMA*. 2021;326(3):230-239. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34283183.
11. Sarilumab (Kevzara) [package insert]. Food and Drug Administration. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761037s001lbl.pdf.
12. Regeneron and Sanofi provide update on U.S. Phase 2/3 adaptive-designed trial of KEVZARA® (sarilumab) in hospitalized COVID-19 patients [press release]. 2020.
13. Tocilizumab (Actemra) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125276s131lbl.pdf.
14. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for actemra (tocilizumab). 2021. Available at: https://www.fda.gov/media/150321/download.
15. Siltuximab (Sylvant) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125496s018lbl.pdf.
16. Baricitinib (Olumiant) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/207924s001lbl.pdf.

17. Food and Drug Administration. Fact sheet for healthcare providers: Emergency Use Authorization (EUA) of baricitinib. 2021. Available at: https://www.fda.gov/media/143823/download.

18. Cao Y, Wei J, Zou L, et al. Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): A multicenter, single-blind, randomized controlled trial. *J Allergy Clin Immunol*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32470486.

19. Guimaraes PO, Quirk D, Furtado RH, et al. Tofacitinib in patients hospitalized with COVID-19 pneumonia. *N Engl J Med*. 2021;385(5):406-415. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34133856.

Antithrombotic Therapy in Patients with COVID-19

Last Updated: February 24, 2022

Summary Recommendations

Chronic Anticoagulant and Antiplatelet Therapy

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends that patients who are receiving anticoagulant or antiplatelet therapies for underlying conditions continue these medications after they receive a diagnosis of COVID-19 **(AIII)**.

Screening and Evaluation for Venous Thromboembolism

- There is currently insufficient evidence to recommend either for or against routine screening for deep vein thrombosis in patients with COVID-19 who do not have signs or symptoms of venous thromboembolism (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 experience an incident thromboembolic event or 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

- The Panel **recommends against** the use of anticoagulants and antiplatelet therapy for the prevention of VTE or arterial thrombosis unless the patient has other indications for the therapy or is participating in a clinical trial **(AIIa)**.
- The Panel **recommends against** routinely continuing VTE prophylaxis after hospital discharge, except in a clinical trial **(AIII)**. For patients who are at high risk for VTE and at low risk of bleeding, extended VTE prophylaxis can be considered, as per the protocol for patients without COVID-19 **(BI)**.

Antithrombotic Therapy for Hospitalized, Nonpregnant Adults Without Evidence of Venous Thromboembolism

- The Panel **recommends against** the use of aspirin to prevent mortality or the need for organ support **(AI)**.
- The Panel recommends that anticoagulant or antiplatelet therapy not be used to prevent arterial thrombosis outside of the usual standard of care for patients without COVID-19 **(AIII)**.
- In hospitalized patients, low molecular weight heparin (LMWH) or unfractionated heparin (UFH) is preferred over oral anticoagulants, because these 2 types of heparin have shorter half-lives and the effect can be reversed quickly, can be administered intravenously or subcutaneously, and have fewer drug-drug interactions **(AIII)**.
- When heparin is used, LMWH is preferred over UFH.

For adults who require low-flow oxygen and do not require intensive care unit (ICU)-level care:

- The Panel recommends 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 bleeding risk **(CIIa)**.
  - Contraindications for the use of therapeutic anticoagulation in patients with COVID-19 are a platelet count <50 x 109/L, hemoglobin <8 g/dL, the need for dual antiplatelet therapy, bleeding within the past 30 days that required an emergency department visit or hospitalization, history of a bleeding disorder, or an inherited or active acquired bleeding disorder. This list is based on the exclusion criteria from clinical trials; patients with these conditions have an increased risk of bleeding.
- In patients without VTE who have begun a therapeutic dose of heparin, treatment should continue for 14 days or until hospital discharge, whichever comes first.
- The Panel recommends the use of a **prophylactic dose** of heparin for patients who are not receiving a therapeutic dose of heparin, unless a contraindication exists **(AIIb)**.

- The Panel **recommends against** the use of a **therapeutic dose** of oral anticoagulants for VTE prophylaxis or prevention of COVID-19 progression, except in a clinical trial **(AIIa)**.
- There is currently insufficient evidence to recommend either for or against the use of thrombolytics for COVID-19.

For adults who require ICU-level care, including those receiving high-flow oxygen:

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

Hospitalized Children

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

Special Considerations During Pregnancy and Lactation

- The Panel recommends that pregnant patients who are receiving anticoagulant or antiplatelet therapies for underlying conditions continue these medications after they receive a diagnosis of COVID-19 **(AIII)**.
- The Panel recommends the use of a **prophylactic dose** of anticoagulation for pregnant patients hospitalized for manifestations of COVID-19, unless otherwise contraindicated **(BIII)**.
- Because pregnant patients have not been included in most clinical trials evaluating therapeutic anticoagulation in the setting of COVID-19, there is currently insufficient evidence to recommend either for or against therapeutic anticoagulation for pregnant patients with COVID-19 without evidence of VTE.
- Like for nonpregnant patients, VTE prophylaxis after hospital discharge is not routinely recommended for pregnant patients **(BIII)**. Decisions to continue VTE prophylaxis in the pregnant or postpartum patient after discharge should be individualized, with consideration of concomitant VTE risk factors.
- Anticoagulation therapy use during labor and delivery requires specialized care and planning. It should be managed in pregnant patients with COVID-19 in a similar way as in pregnant patients with other conditions **(AIII)**.
- UFH, LMWH, and warfarin do not accumulate in breast milk and do not induce an anticoagulant effect in the newborn; therefore, they can be used by breastfeeding individuals who require VTE prophylaxis or treatment **(AIII)**.

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

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

Association Between COVID-19 and Thromboembolism

COVID-19 has been associated with inflammation and a prothrombotic state, with increases in fibrin, fibrin degradation products, fibrinogen, and D-dimer levels.[1,2] In some studies, elevations in these markers have been associated with worse clinical outcomes.[3,4]

Studies have reported varying incidences of venous thromboembolism (VTE) in patients with COVID-19. A meta-analysis of studies of hospitalized patients with COVID-19 treated with VTE prophylaxis found an overall VTE prevalence of 14.1% (95% CI, 11.6–16.9).[5] The VTE prevalence was higher in studies that used ultrasound screening (40.3%; 95% CI, 27.0–54.3) than in studies that did not (9.5%; 95% CI, 7.5–11.7). In randomized controlled trials conducted prior to the pandemic, the incidence of VTE in hospitalized patients without COVID-19 who received VTE prophylaxis ranged from 0.3% to 1% for symptomatic VTE and from 2.8% to 5.6% for VTE overall.[6-8] The VTE incidence in randomized trials in critically ill patients without COVID-19 who received a prophylactic dose of anticoagulants ranged from 5% to 16%, and a prospective cohort study of critically ill patients with sepsis reported a VTE incidence of 37%.[9-12]

Guidelines about coagulopathy and the prevention and management of VTE in patients with COVID-19 have been released by multiple organizations, including the American College of Chest Physicians,[13] American Society of Hematology,[14] Anticoagulation Forum,[15] International Society on Thrombosis and Haemostasis,[16] Italian Society for Haemostasis and Thrombosis,[17] National Institute for Health and Care Excellence (NICE),[18] and Royal College of Physicians.[19]

The guidelines referenced above agree that hospitalized, nonpregnant patients with COVID-19 should receive, at a minimum, a prophylactic dose of anticoagulation to prevent VTE. The NICE guideline recommendation states: "Consider a treatment dose of a low-molecular-weight heparin (LMWH) for young people and adults with COVID-19 who need low-flow oxygen and who do not have an increased bleeding risk." Results from clinical trials that assess the safety and efficacy of different anticoagulant doses and strategies have provided further information on antithrombotic strategies for patients with COVID-19.

Chronic Anticoagulant or Antiplatelet Therapy

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. Patients with a mechanical heart valve, ventricular assist device, valvular atrial fibrillation, or antiphospholipid antibody syndrome or who are lactating should not discontinue treatment with warfarin **(AIII)**. The COVID-19 Treatment Guidelines Panel (the Panel) recommends that hospitalized patients with COVID-19 who are receiving anticoagulant or antiplatelet therapy for underlying medical conditions continue this treatment unless significant bleeding develops or other contraindications are present **(AIII)**.

Screening and Evaluation for Venous Thromboembolism

VTE guidelines for patients without COVID-19 have recommended against routine screening ultrasounds in critically ill patients because no study has shown that this strategy reduces the rate of subsequent symptomatic thromboembolic complications.[20] Although the incidence of thromboembolic events, especially pulmonary emboli, can be high among hospitalized patients with COVID-19, no published data demonstrate the clinical utility of using lower extremity ultrasound as routine surveillance for deep vein thrombosis in this population.

- There is currently insufficient evidence to recommend either for or against routine screening for deep vein thrombosis 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 experience an incident thromboembolic event or 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 interactions. In hospitalized, critically ill patients, LMWH or unfractionated heparin (UFH) is preferred over oral anticoagulants, because these 2 types of heparin have shorter half-lives and the effect can be reversed quickly, can be administered intravenously or subcutaneously, and have fewer drug-drug interactions **(AIII)**.

Management of Nonhospitalized Patients

The ACTIV-4b placebo-controlled, randomized trial evaluated the efficacy of aspirin versus prophylactic (2.5 mg) or therapeutic (5 mg) doses of apixaban to prevent thromboembolic events, hospitalization, and mortality in outpatients >40 years with COVID-19. The trial was stopped in June 2021 due to a low event rate (1 patient each in the placebo, aspirin, and apixaban 2.5 mg arms and 2 patients in the apixaban 5 mg arm) after randomization of 657 symptomatic outpatients. The median time from randomization to study treatment was 3 days, and 22 participants were hospitalized for COVID-19 prior to initiation of study drug.[21] It is not known whether patients with previous VTE events or inherited thrombophilias were included in this trial. For nonhospitalized patients with COVID-19, the Panel **recommends against** the use of anticoagulants and antiplatelet therapy for the prevention of VTE or arterial thrombosis unless the patient has other indications for the therapy or is participating in a clinical trial **(AIIa)**.

Management of Hospitalized Patients

Several studies have evaluated the risks and benefits of prophylactic and therapeutic doses of anticoagulants in patients with COVID-19. Observational studies and clinical trials have examined the effects of anticoagulation on mortality, progression of COVID-19, thrombosis, and bleeding. Some of these studies are outlined below (visit ClinicalTrials.gov for a current list of trials). Observational studies are included here only when evidence from clinical trials is not available.

Prophylactic-Dose of Anticoagulation Versus No Anticoagulation—Observational Cohort

An observational study of 4,297 veterans hospitalized with COVID-19 evaluated the benefit of prophylactic anticoagulation. A prophylactic dose of anticoagulation was administered to 3,627 patients with COVID-19 within 24 hours of hospital admission. An inverse probability of treatment weighted analysis showed a cumulative 30-day mortality of 14% among veterans who received prophylactic anticoagulation and 19% among patients who were not treated with anticoagulation (HR 0.73; 95% CI, 0.66–0.81). Participants treated with the prophylactic dose did not have a significant difference in risk of bleeding that required transfusion when compared with participants who were not treated (HR 0.87; 95% CI, 0.71–1.05). Overall, the study demonstrated that patients with COVID-19 may benefit from a prophylactic dose of anticoagulation.[22]

Therapeutic Versus Prophylactic Doses of Heparin in Hospitalized Patients Who Do Not Require Intensive Care Unit-Level Care

Several randomized controlled trials have evaluated the role of therapeutic doses of heparin in reducing VTE events or mortality in patients hospitalized for COVID-19.

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 5. The inclusion and exclusion criteria for these studies varied, but most included a need for supplemental oxygen and no risk

of a major bleeding event. In the larger multiplatform trial, therapeutic doses of heparin increased organ support-free days but did not significantly affect mortality or length of hospitalization when compared with prophylactic doses of heparin.[23]

The RAPID trial enrolled patients with elevated D-dimer levels and hypoxemia. The patients were randomized to receive therapeutic or prophylactic doses of heparin. There was no statistically significant difference between the arms for the primary endpoint, which was a composite of intensive care unit (ICU) admission, noninvasive or mechanical ventilation, or death by Day 28. However, the therapeutic dose of heparin reduced all-cause death, a secondary outcome.[24]

The HEP-COVID trial enrolled patients who required supplemental oxygen and had a D-dimer value >4 times the upper limit of normal (ULN) or a sepsis-induced coagulopathy score of ≥4. There were significantly fewer occurrences of the primary endpoint of VTE, arterial thromboembolism, or all-cause death within 32 days of randomization in the therapeutic LMWH arm than in the prophylactic LMWH arm, but there was no difference between arms for the outcome of death within 32 days.[25] Results from smaller randomized trials, single-center studies, and observational studies have also been published.

Given the results of the ATTACC/ACTIV-4a/REMAP-CAP, RAPID, and HEP-COVID trials conducted among hospitalized, nonpregnant adults with COVID-19 who did not require ICU-level care and without evidence of VTE:

- The Panel recommends 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 bleeding risk **(CIIa)**.
  - Based on clinical trial exclusion criteria, contraindications for use of therapeutic anticoagulation for patients with COVID-19 are a platelet count <50 x 109/L, hemoglobin <8 g/dL, the need for dual antiplatelet therapy, bleeding within the past 30 days that required an emergency department visit or hospitalization, history of a bleeding disorder, or an inherited or active, acquired bleeding disorder.
- LMWH is preferred over UFH because of its decreased administrative burden and because LMWH was the predominant form of heparin used in the clinical trials for COVID-19.
- In patients without VTE who have begun a therapeutic dose of heparin, treatment should continue for 14 days or until hospital discharge, whichever comes first.
- Patients with predicted hospitalizations of <72 hours were excluded from the multiplatform trial. The risk/benefit ratio of therapeutic doses of anticoagulation for short hospital stays is not known.
- The Panel recommends 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 prevention of COVID-19 progression, except in a clinical trial **(AIIa)**.
- There is currently insufficient evidence to recommend either for or against the use of thrombolytics for COVID-19.

Prophylactic Versus Intermediate or Therapeutic Doses of Heparin in Hospitalized Patients Who Require Intensive Care Unit-Level Care

Several randomized controlled trials have evaluated the role of therapeutic doses of heparin in reducing VTE events or mortality in patients in the ICU setting. Clinical data for these trials are summarized in Table 5.

For the composite endpoint of adjudicated VTE, arterial thrombosis, ECMO, or all-cause mortality, the INSPIRATION trial found no difference between patients in the ICU treated with an intermediate dose of anticoagulation (enoxaparin 1 mg/kg daily) and those who received a prophylactic dose (45.7% vs. 44.1%; OR 1.06; 95% CI, 0.76–1.48). Major bleeding occurred in 2.5% of patients in the intermediate-dose anticoagulation arm compared with 1.4% of patients who received the prophylactic dose. Overall, there was no significant benefit of receiving an intermediate dose of anticoagulation for patients with COVID-19 in the ICU.[26]

A multiplatform randomized control trial (REMAP-CAP/ACTIV-4a/ATTACC) compared the effectiveness of a therapeutic dose of heparin or LMWH with usual care in reducing the number of organ support-free days among critically ill patients with COVID-19.[27] All 3 trials were stopped for futility. Heparin doses in the usual care arm varied. The median number of organ support-free days was 3 days (IQR -1 to 16) for patients who received a therapeutic dose of anticoagulation and 4 days (IQR -1 to 16) for patients who received usual care. The likelihood of survival to hospital discharge did not differ between arms (63% therapeutic arm vs. 65% usual care arm; aOR 0.84; 95% CrI, 0.64–1.11). Major bleeding occurred in 4% of participants receiving therapeutic anticoagulation and in 2% of participants receiving usual care. Therapeutic doses of heparin showed no significant benefit for patients with COVID-19 admitted to the ICU.

Given the results of these trials, for hospitalized, nonpregnant adults with COVID-19 who require ICU level-care and who do not have documented or suspected VTE:

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

Rivaroxaban Versus Usual Care in Hospitalized Patients With Elevated D-Dimer Levels

The ACTION trial randomized adults hospitalized with COVID-19 and elevated D-dimer levels (defined as above the laboratory ULN) to receive rivaroxaban 20 mg daily for 30 days or usual care[28] (see Table 5 for a summary of clinical data for this trial). No statistical difference was found for the composite endpoint of time to death, hospitalization duration, and oxygen use duration (hierarchical analysis; win ratio 0.86; 95% CI, 0.59–1.22) or for the individual components. The probability of clinically relevant nonmajor bleeding was greater with rivaroxaban (5% rivaroxaban arm vs. 1% usual care arm; relative risk 5.23; 95% CI, 1.54–17.77), but for major bleeding events the difference between arms was not significant (3% rivaroxaban arm vs. 1% usual care arm; relative risk 2.45; 95% CI, 0.78–7.73).

Given the lack of benefit and the increased risk of bleeding events, the Panel **recommends against** the use of a **therapeutic dose** of anticoagulation for VTE prophylaxis and prevention of COVID-19 progression, except in a clinical trial **(BI)**.

Aspirin Versus Usual Care in Hospitalized Patients

The RECOVERY trial randomized 7,351 hospitalized adults with COVID-19 to usual care plus aspirin 150 mg per day and 7,541 patients to usual care only.[29] Mortality at 28 days was 17% in both arms (rate ratio 0.96; 95% CI, 0.89–1.04). Results were similar in all prespecified subgroups, including when restricted to patients with polymerase chain reaction–documented SARS-CoV-2 infection. Among participants not receiving mechanical ventilation at baseline, there was no difference in progression

to mechanical ventilation or death (21% aspirin arm vs. 22% usual care arm; rate ratio 0.96; 95% CI, 0.90–1.03). Among those treated with aspirin, the incidence of thrombotic events was lower (4.6% vs. 5.3%; absolute difference 0.6%; SE 0.4%), and the incidence of major bleeding events was higher (1.6% vs. 1.0%; absolute difference 0.6%; SE 0.2%). Given the large trial size, lack of mortality benefit, and increase in bleeding events, the Panel **recommends against** the use of aspirin to prevent mortality or the need for organ support in hospitalized patients with COVID-19 **(AI)**.

P2Y12 Inhibitor Versus Usual Care in Hospitalized Patients

The ACTIV-4a trial evaluated P2Y12 inhibitor therapy plus a therapeutic dose of heparin versus therapeutic heparin alone in noncritically ill, hospitalized patients with COVID-19. In this study, enrollment in the cohort that did not receive intensive care was stopped due to futility because the combination therapy did not improve the number of organ support-free days.[30]

Thrombolytic Therapy

Clinical trials are evaluating the use of thrombolysis on mortality and the progression of COVID-19 illness. There is currently insufficient evidence to recommend either for or against the use of thrombolytic agents for VTE prophylaxis for hospitalized patients with COVID-19 outside of a clinical trial.

Hospitalized Children

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

Patients Discharged From the Hospital

For certain high-VTE risk patients without COVID-19, post-discharge prophylaxis has been shown to be beneficial. The Food and Drug Administration approved the use of rivaroxaban 10 mg daily for 31 to 39 days in these patients.[32,33] Inclusion criteria for the trials that studied post-discharge VTE prophylaxis included:

- A VTE risk score of ≥4 on the modified International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) tool,[34] *or*
- A VTE risk score ≥2 on the modified IMPROVE tool[35] and a D-dimer level >2 times ULN.[32]

Any decision to use post-discharge VTE prophylaxis for patients with COVID-19 should include consideration of the individual patient's risk factors for VTE, bleeding risks, and feasibility. The MICHELLE trial of post-discharge prophylaxis in patients with COVID-19 was recently published and is being reviewed by the Panel.[36] Participation in clinical trials is encouraged.

Special Considerations During Pregnancy and Lactation

Because pregnancy is a hypercoagulable state, the risk of thromboembolism is greater in pregnant individuals than in nonpregnant individuals.[37] 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.[38-40] The American College of Obstetricians and Gynecologists (ACOG) advises that, although there are no data for or against thromboprophylaxis in the setting of COVID-19 in pregnancy, VTE prophylaxis can reasonably be considered for pregnant individuals hospitalized with COVID-19, particularly for those who have severe

disease.[41] If there are no contraindications to use, the Society for Maternal-Fetal Medicine recommends prophylactic heparin or LMWH in critically ill or mechanically ventilated pregnant patients.[42] 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.[43,44] If delivery is imminent, or if there are other risks for bleeding, the risk of bleeding may outweigh the potential benefit of VTE prophylaxis in pregnancy.

Outside of pregnancy, D-dimer levels have been used to stratify VTE risk. However, physiologic increases in D-dimer levels may occur during pregnancy, making elevated D-dimer values an unreliable predictor that should not be used to evaluate VTE risk during pregnancy in the setting of COVID-19.[45-47]

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.[44] Direct-acting anticoagulants are not routinely recommended during pregnancy because of a lack of safety data for pregnant individuals.[43] 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 hospitalized for manifestations of COVID-19, unless otherwise contraindicated **(BIII)**.
- Because pregnant patients have not been included in most clinical trials evaluating therapeutic anticoagulation in the setting of COVID-19, there is currently insufficient evidence to recommend either for or against therapeutic anticoagulation for pregnant patients with COVID-19 without evidence of VTE.
- Like for nonpregnant patients, VTE prophylaxis after hospital discharge is not routinely recommended for pregnant patients **(BIII)**. Decisions to continue VTE prophylaxis in the pregnant or postpartum patient after discharge should be individualized, with consideration of concomitant VTE risk factors.
- Anticoagulation therapy use during labor and delivery requires specialized care and planning. It should be managed in pregnant patients with COVID-19 in a similar way as in pregnant patients with other conditions **(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)**.

References

1. Han H, Yang L, Liu R, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. *Clin Chem Lab Med*. 2020;58(7):1116-1120. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32172226.
2. Driggin E, Madhavan MV, Bikdeli B, et al. Cardiovascular considerations for patients, health care workers, and health systems during the COVID-19 pandemic. *J Am Coll Cardiol*. 2020;75(18):2352-2371. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32201335.
3. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382(18):1708-1720. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32109013.

4. Tang N, Bai H, Chen X, et al. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost*. 2020;18(5):1094-1099. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32220112.
5. Nopp S, Moik F, Jilma B, Pabinger I, Ay C. Risk of venous thromboembolism in patients with COVID-19: a systematic review and meta-analysis. *Res Pract Thromb Haemost*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33043231.
6. Cohen AT, Davidson BL, Gallus AS, et al. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. *BMJ*. 2006;332(7537):325-329. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16439370.
7. Leizorovicz A, Cohen AT, Turpie AG, et al. Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. *Circulation*. 2004;110(7):874-879. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15289368.
8. Samama MM, Cohen AT, Darmon JY, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in Medical Patients with Enoxaparin Study Group. *N Engl J Med*. 1999;341(11):793-800. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10477777.
9. Fraisse F, Holzapfel L, Couland JM, et al. Nadroparin in the prevention of deep vein thrombosis in acute decompensated COPD. The Association of Non-University Affiliated Intensive Care Specialist Physicians of France. *Am J Respir Crit Care Med*. 2000;161(4 Pt 1):1109-1114. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10764298.
10. PROTECT Investigators for the Canadian Critical Care Trials Group, Australian t, New Zealand Intensive Care Society Clinical Trials Group, et al. Dalteparin versus unfractionated heparin in critically ill patients. *N Engl J Med*. 2011;364(14):1305-1314. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21417952.
11. Shorr AF, Williams MD. Venous thromboembolism in critically ill patients. Observations from a randomized trial in sepsis. *Thromb Haemost*. 2009;101(1):139-144. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19132200.
12. Kaplan D, Casper TC, Elliott CG, et al. VTE incidence and risk factors in patients with severe sepsis and septic shock. *Chest*. 2015;148(5):1224-1230. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26111103.
13. Moores LK, Tritschler T, Brosnahan S, et al. Thromboprophylaxis in patients with COVID-19. A brief update to the CHEST Guideline and expert panel report. *Chest*. 2022;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35167861.
14. American Society of Hematology. ASH guidelines on use of anticoagulation in patients with COVID-19. 2022. Available at: https://www.hematology.org/education/clinicians/guidelines-and-quality-care/clinical-practice-guidelines/venous-thromboembolism-guidelines/ash-guidelines-on-use-of-anticoagulation-in-patients-with-covid-19. Accessed February 3, 2022.
15. Barnes GD, Burnett A, Allen A, et al. Thromboembolism and anticoagulant therapy during the COVID-19 pandemic: interim clinical guidance from the anticoagulation forum. *J Thromb Thrombolysis*. 2020;50(1):72-81. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32440883.
16. Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost*. 2020;18(5):1023-1026. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32338827.
17. Marietta M, Ageno W, Artoni A, et al. COVID-19 and haemostasis: a position paper from Italian Society on Thrombosis and Haemostasis (SISET). *Blood Transfus*. 2020;18(3):167-169. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32281926.
18. National Institute for Health Care Excellence. COVID-19 rapid guideline: managing COVID-19. 2022. Available at: https://www.nice.org.uk/guidance/ng191. Accessed February 3, 2022.
19. Royal College of Physicians. Clinical guide for the prevention, detection and management of thromboembolic

disease in patients with COVID-19. 2020. Available at: https://icmanaesthesiacovid-19.org/clinical-guide-prevention-detection-and-management-of-vte-in-patients-with-covid-19. Accessed February 4, 2022.

20. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 Suppl):e195S-e226S. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22315261.
21. Connors JM, Brooks MM, Sciurba FC, et al. Effect of antithrombotic therapy on clinical outcomes in outpatients with clinically stable symptomatic COVID-19: the ACTIV-4B randomized clinical trial. *JAMA*. 2021;326(17):1703-1712. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34633405.
22. Rentsch CT, Beckman JA, Tomlinson L, et al. Early initiation of prophylactic anticoagulation for prevention of coronavirus disease 2019 mortality in patients admitted to hospital in the United States: cohort study. *BMJ*. 2021;372:n311. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33574135.
23. ATTACC Investigators, ACTIV-4a Investigators, REMAP-CAP Investigators, et al. Therapeutic anticoagulation with heparin in noncritically ill patients with COVID-19. *N Engl J Med*. 2021;385(9):790-802. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34351721.
24. Sholzberg M, Tang GH, Rahhal H, et al. Effectiveness of therapeutic heparin versus prophylactic heparin on death, mechanical ventilation, or intensive care unit admission in moderately ill patients with COVID-19 admitted to hospital: RAPID randomised clinical trial. *BMJ*. 2021;375:n2400. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34649864.
25. Spyropoulos AC, Goldin M, Giannis D, et al. Efficacy and safety of therapeutic-dose heparin vs standard prophylactic or intermediate-dose heparins for thromboprophylaxis in high-risk hospitalized patients with COVID-19: the HEP-COVID randomized clinical trial. *JAMA Intern Med*. 2021;181(12):1612-1620. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34617959.
26. Inspiration Investigators, Sadeghipour P, Talasaz AH, et al. Effect of intermediate-dose vs standard-dose prophylactic anticoagulation on thrombotic events, extracorporeal membrane oxygenation treatment, or mortality among patients with COVID-19 admitted to the intensive care unit: the INSPIRATION randomized clinical trial. *JAMA*. 2021;325(16):1620-1630. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33734299.
27. The REMAP-CAP, ACTIV-4a, ATTACC Investigators, Zarychanski R. Therapeutic anticoagulation in critically ill patients with COVID-19—preliminary report. *medRxiv*. 2021;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.03.10.21252749v1.
28. Lopes RD, de Barros ESPGM, Furtado RHM, et al. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. *Lancet*. 2021;397(10291):2253-2263. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34097856.
29. RECOVERY Collaborative Group. Aspirin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. 2022;399(10320):143-151. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34800427.
30. Berger JS, Kornblith LZ, Gong MN, et al. Effect of P2Y12 inhibitors on survival free of organ support among non-critically ill hospitalized patients with COVID-19: a randomized clinical trial. *JAMA*. 2022;327(3):227-236. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35040887.
31. Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. *Acta Paediatr*. 2020;109(6):1088-1095. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32202343.
32. Spyropoulos AC, Lipardi C, Xu J, et al. Modified IMPROVE VTE risk score and elevated D-dimer identify a high venous thromboembolism risk in acutely ill medical population for extended thromboprophylaxis. *TH Open*. 2020;4(1):e59-e65. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32190813.
33. Cohen AT, Harrington RA, Goldhaber SZ, et al. Extended thromboprophylaxis with betrixaban in acutely ill medical patients. *N Engl J Med*. 2016;375(6):534-544. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27232649.

34. Spyropoulos AC, Anderson FA, Jr., FitzGerald G, et al. Predictive and associative models to identify hospitalized medical patients at risk for VTE. *Chest*. 2011;140(3):706-714. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21436241.

35. Gibson CM, Spyropoulos AC, Cohen AT, et al. The IMPROVEDD VTE risk score: incorporation of d-dimer into the IMPROVE score to improve venous thromboembolism risk stratification. *TH Open*. 2017;1(1):e56-e65. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31249911.

36. Ramacciotti E, Barile Agati L, Calderaro D, et al. Rivaroxaban versus no anticoagulation for post-discharge thromboprophylaxis after hospitalisation for COVID-19 (MICHELLE): an open-label, multicentre, randomised, controlled trial. *Lancet*. 2022;399(10319):50-59. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34921756.

37. Heit JA, Kobbervig CE, James AH, et al. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. *Ann Intern Med*. 2005;143(10):697-706. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16287790.

38. Breslin N, Baptiste C, Gyamfi-Bannerman C, et al. Coronavirus disease 2019 infection among asymptomatic and symptomatic pregnant women: two weeks of confirmed presentations to an affiliated pair of New York City hospitals. *Am J Obstet Gynecol MFM*. 2020;2(2):100118. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32292903.

39. Knight M, Bunch K, Vousden N, et al. Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study. *BMJ*. 2020;369:m2107. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32513659.

40. Delahoy MJ, Whitaker M, O'Halloran A, et al. Characteristics and maternal and birth outcomes of hospitalized pregnant women with laboratory-confirmed COVID-19 - COVID-NET, 13 States, March 1–August 22, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(38):1347-1354. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32970655.

41. The American College of Obstetricians and Gynecologists. COVID-19 FAQs for obstetrician-gynecologists, obstetrics. 2020. Available at: https://www.acog.org/clinical-information/physician-faqs/covid-19-faqs-for-ob-gyns-obstetrics. Accessed February 4, 2022.

42. Society for Maternal Fetal Medicine. Management considerations for pregnant patients With COVID-19. 2020. Available at: https://s3.amazonaws.com/cdn.smfm.org/media/2336/SMFM_COVID_Management_of_COVID_pos_preg_patients_4-30-20_final.pdf.

43. Bates SM, Rajasekhar A, Middeldorp S, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy. *Blood Adv*. 2018;2(22):3317-3359. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30482767.

44. ACOG practice bulletin no. 196 summary: thromboembolism in pregnancy. *Obstet Gynecol*. 2018;132(1):243-248. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29939933.

45. Wang M, Lu S, Li S, Shen F. Reference intervals of D-dimer during the pregnancy and puerperium period on the STA-R evolution coagulation analyzer. *Clin Chim Acta*. 2013;425:176-180. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23954836.

46. Reger B, Peterfalvi A, Litter I, et al. Challenges in the evaluation of D-dimer and fibrinogen levels in pregnant women. *Thromb Res*. 2013;131(4):e183-187. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23481480.

47. Hu W, Wang Y, Li J, et al. The predictive value of D-dimer test for venous thromboembolism during puerperium: a prospective cohort study. *Clin Appl Thromb Hemost*. 2020;26:1076029620901786. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32090610.

Table 5. Antithrombotic Therapy: Selected Clinical Data

Last Updated: February 24, 2022

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

Methods	Results	Limitations and Interpretation
ATTACC/ACTIV-4a/REMAP-CAP: Multiplatform, Open-Label RCT of Therapeutic Anticoagulation in Noncritically Ill, Hospitalized Patients With COVID-19 in 9 Countries[1]		

Key Inclusion Criteria:
• Hospitalized with laboratory-confirmed SARS-CoV-2 infection without need for HFNC oxygen, NIV, MV, vasopressors, or inotropes
Key Exclusion Criteria:
• Discharge expected ≤72 hours
• Requirement for therapeutic anticoagulation or dual antiplatelet therapy
• High bleeding risk
Interventions:
• Therapeutic UFH or LMWH for 14 days or until discharge, whichever comes first (n = 1,190)
• SOC (n = 1,054)
Primary Endpoint:
• Organ support-free days at Day 21, evaluated on an ordinal scale
Key Secondary Endpoints:
• Survival until hospital discharge
• Hospital LOS
• Thrombosis or major bleeding
	Participant Characteristics:
	• Median age 59 years; 59% men; median BMI 30
	• 52% with HTN; 30% with DM; 11% with CVD
	• 66% required low-flow oxygen
	• D-dimer:
	  • 48.4% <2 times ULN
	  • 28.4% ≥2 times ULN
	  • 23.1% unknown
	• 62% on corticosteroids; 36% on RDV
	Primary Outcomes:
	• Organ support-free days: therapeutic anticoagulation superior to SOC (aOR 1.27; 95% CrI, 1.03–1.58; 99% posterior probability)
	• Survival until hospital discharge without organ support: 4% absolute difference favoring therapeutic anticoagulation arm (95% CrI, 0.5–7.2)
	• Outcome consistent across D-dimer stratum
	Secondary Outcomes:
	• Survival until hospital discharge: 92% in both arms
	• Hospital LOS: no difference between arms (aOR 1.03; 95% CrI, 0.94–1.13)
	• Thrombosis: 1% in therapeutic arm vs. 2% in SOC arm
	• Major bleeding: 2% in therapeutic arm vs. 1% in SOC arm
		Key Limitations:
		• Open-label study
		• Anticoagulation dose varied in SOC arm (27% received intermediate-dose thromboprophylaxis).
		• Studies had different criteria for ICU care and expected hospital LOS.
		• Only enrolled 17% of screened patients
		Interpretation:
		• Therapeutic heparin increased organ support-free days and decreased the number of patients requiring organ support.
		• Therapeutic heparin did not significantly affect hospital LOS or the number of major thrombosis events or deaths.
		• Major bleeds occurred 1% more frequently in therapeutic arm than in SOC arm.

Methods	Results	Limitations and Interpretation
RAPID: Open-Label RCT of Therapeutic Heparin in Moderately Ill, Hospitalized Patients With COVID-19 in 6 Countries[2]		

Key Inclusion Criteria:
• Hospitalized with COVID-19 and D-dimer ≥2 times ULN or any elevated D-dimer level and SpO_2 ≤93% on room air
• Hospitalized <5 days
Key Exclusion Criteria:
• Indication for therapeutic anticoagulation
• Dual antiplatelet therapy
• High bleeding risk
Interventions:
• Therapeutic UFH or LMWH for 28 days or until discharge or death (n = 228)
• Prophylactic UFH or LMWH for 28 days or until discharge or death (n = 237)
Primary Endpoint:
• Composite of ICU admission, NIV or MV, or death up to 28 days
Key Secondary Endpoints:
• All-cause death
• Mean organ support-free days
• VTE
• Major bleeding event
• Mean hospital-free days alive
	Participant Characteristics:
	• Median age 60 years; 57% men; mean BMI 30
	• 48% with HTN; 34% with DM; 7% with CVD
	• 91% had hypoxia; 6% received HFNC oxygen
	• D-dimer:
	  • 49% <2 times ULN
	  • 51% ≥2 times ULN
	• 69% on corticosteroids
	Primary Outcome:
	• ICU admission, NIV or MV, or death: 16% in therapeutic arm vs. 22% in prophylactic arm (OR 0.69; 95% CI, 0.43–1.10)
	Secondary Outcomes:
	• All-cause death: 2% in therapeutic arm vs. 8% in prophylactic arm (OR 0.22; 95% CI, 0.07–0.65)
	• Mean organ support-free days: 26 days in therapeutic arm vs. 24 days in prophylactic arm (OR 1.41; 95% CI, 0.9–2.21)
	• No difference between arms for VTE (1% in therapeutic arm vs. 3% in prophylactic arm) or major bleeding (1% in therapeutic arm vs. 2% in prophylactic arm)
	• Mean hospital-free days alive: 20 days in therapeutic arm vs. 18 days in prophylactic arm (OR 1.09; 95% CI, 0.79–1.50)
		Key Limitations:
		• Open-label study
		• Only enrolled 12% of screened patients
		Interpretation:
		• Compared to prophylactic heparin, therapeutic heparin reduced mortality (a secondary endpoint) but had no effects on the composite primary endpoint of ICU admissions or the need for NIV or MV, or death up to 28 days.
		• Major bleeding and VTE events were not different in the therapeutic and prophylactic arms.

Methods	Results	Limitations and Interpretation
HEP-COVID: Open-Label RCT of Therapeutic Heparin in High-Risk, Hospitalized Patients With COVID-19 in the United States[3]		

Key Inclusion Criteria:
• Hospitalized with supplemental oxygen
• D-dimer >4 times ULN or sepsis-induced coagulopathy score of ≥4
• Hospitalized <72 hours
Key Exclusion Criteria:
• Indication for therapeutic anticoagulation
• Dual antiplatelet therapy
• High bleeding risk
• CrCl <15 mL/min
Interventions:
• Therapeutic LMWH until hospital discharge or primary endpoint met (n = 129)
• Usual care of prophylactic or intermediate-dose LMWH until hospital discharge or primary endpoint met (n = 124)
Primary Endpoint:
• Composite of VTE, ATE, or death of any cause within 32 days of randomization
Key Safety Endpoint:
• Major bleeding
	Participant Characteristics:
	• Median age 67 years; 54% men; mean BMI 30
	• 60% with HTN; 37% with DM; 7% with CVD
	• 64% received oxygen via nasal cannula; 15% received high-flow oxygen or NIV; 5% received MV
	• 80% on corticosteroids
	Primary Outcomes:
	• Composite of VTE, ATE, and death within 32 days: 29% in therapeutic arm vs. 42% in usual care arm (relative risk 0.68; 95% CI, 0.49–0.96)
	  • Death: 19% in therapeutic arm vs. 25% in usual care arm (relative risk 0.78; 95% CI, 0.49–1.23)
	  • Thrombotic events: 11% in therapeutic arm vs. 29% in usual care arm (relative risk 0.37; 95% CI, 0.21–0.66
	• Non-ICU stratum composite of VTE, ATE, or death within 32 days: 17% in therapeutic arm vs. 36% in usual care arm (relative risk 0.46; 95% CI, 0.27–0.81)
	Safety Outcomes:
	• Major bleeding: 5% in therapeutic arm vs. 2% in usual care arm (relative risk 2.88, 95% CI, 0.59–14.02)
	• Non-ICU stratum major bleeding: 2% in both arms
		Key Limitations:
		• Open-label study
		• Only enrolled 2% of screened patients
		Interpretation:
		• Compared to usual care, therapeutic LMWH reduced the incidence of VTE, ATE, and death.
		• For patients not in the ICU, therapeutic LMWH significantly reduced thrombotic events and did not increase major bleeding.

Methods	Results	Limitations and Interpretation
ACTION: Open-Label RCT of Therapeutic Oral Anticoagulation (Rivaroxaban) in Hospitalized Patients With COVID-19 in Brazil[4]		

Key Inclusion Criteria:
• Hospitalized for COVID-19 with elevated D-dimer level
• Symptoms for ≤14 days
Key Exclusion Criteria:
• Indication for therapeutic anticoagulation
• CrCl <30 mL/min
• P2Y12 inhibitor therapy or aspirin >100 mg
• High bleeding risk
Interventions:
• Therapeutic anticoagulation for 30 days: rivaroxaban 15 mg or 20 mg daily; if clinically unstable, enoxaparin 1 mg/kg twice daily or UFH (n = 311)
• Usual care prophylactic anticoagulation with enoxaparin or UFH during hospitalization (n = 304)
Primary Endpoint:
• Hierarchical composite of time to death, hospital duration, and oxygen use duration through Day 30
Key Secondary Endpoints:
• Thrombosis, with and without all-cause death
• Mortality
• Bleeding events
	Participant Characteristics:
	• Median age 57 years; 60% men; mean BMI 30
	• 49% with HTN; 24% with DM; 5% with coronary disease
	• Critically ill: 7% in therapeutic arm; 5% in usual care arm
	• 75% required oxygen: 60% low-flow oxygen; 8% HFNC oxygen; 1% NIV; 6% MV
	• 83% on corticosteroids
	Primary Outcomes:
	• Composite of time to death, hospital duration, and oxygen use duration: no difference between arms (win ratio 0.86; 95% CI, 0.59–1.22)
	Secondary Outcomes:
	• No difference between therapeutic and prophylactic arms:
	  • Mortality: 11% vs. 8%
	  • Thrombosis: 7% vs. 10%
	• Any bleeding: 12% in therapeutic arm vs. 3% in usual care arm
	• Major bleeding: 3% in therapeutic arm vs. 1% in usual care arm
	• Clinically relevant, nonmajor bleeding: 5% in therapeutic arm vs. 1% in usual care arm
		Key Limitations:
		• Open-label study
		• Only enrolled 18% of screened patients
		• Longer duration of anticoagulation in the rivaroxaban arm (30 days) than the prophylactic anticoagulation arm (mean duration = 8 days)
		Interpretation:
		• When compared with usual care, therapeutic rivaroxaban did not reduce mortality, hospital duration, oxygen use duration, or thrombosis.
		• Patients who received therapeutic rivaroxaban had more clinically relevant nonmajor bleeding than those who received usual care.
		• The longer duration of therapy in the rivaroxaban arm may have influenced the difference in bleeding events.

Methods	Results	Limitations and Interpretation
REMAP-CAP/ACTIV-4a/ATTACC: Multiplatform, Open-Label RCT of Therapeutic Anticoagulation in Critically Ill, Hospitalized Patients With COVID-19 in 20 Countries[5]		

Key Inclusion Criteria:
• Hospitalized with severe COVID-19 and receiving HFNC oxygen, NIV, MV, ECMO, vasopressors, or inotropes
• Hospitalized <72 hours (ACTIV-4a, ATTACC) or <14 days (REMAP-CAP)
Key Exclusion Criteria:
• Discharge expected within 72 hours
• Requirement for therapeutic anticoagulation or dual antiplatelet therapy
• High bleeding risk
Interventions:
• Therapeutic UFH or LMWH for 14 days or until discharge, whichever comes first (n = 534)
• Usual care (n = 564)
Primary Endpoint:
• Organ support-free days at Day 21
Key Secondary Endpoints:
• Survival to hospital discharge
• Any thrombosis
• Composite of major thrombotic events or death
• Bleeding events
	Participant Characteristics:
	• Median age 60 years; 70% men; median BMI 30
	• 24% with chronic respiratory disease; 33% with DM; 10% with chronic kidney disease; 8% with severe CVD
	• 32% required HFNC oxygen; 38% required NIV; 29% required MV
	• 18% on vasopressors; 82% on corticosteroids; 32% on RDV
	Primary Outcome:
	• Median organ support-free days at Day 21: 4 days therapeutic arm vs. 5 days usual care arm (aOR 0.83; 95% CrI, 0.67–1.03; 99.9% posterior probability of futility; OR < 1.2)
	Secondary Outcomes:
	• No difference between therapeutic and usual care arms:
	  • Survival to hospital discharge: 63% vs. 65% (aOR 0.84; 95% CrI, 0.64–1.11)
	  • Thrombosis: 6% vs. 10%
	  • Major thrombotic events or death: 41% both arms
	  • Major bleeding events: 4% vs. 2% (aOR 1.48; 95% CrI, 0.75–3.04)
		Key Limitations:
		• Open-label study
		• Anticoagulation dose varied in usual care arm (i.e., 51% intermediate, 2% subtherapeutic, 5% therapeutic).
		• Inclusion criteria for hospital LOS and ICU-level care differed across trials.
		• Trial stopped for futility.
		Interpretation:
		• In patients requiring ICU care, therapeutic heparin did not reduce the duration of organ support or mortality.
		• Although the differences were nonsignificant, patients who received therapeutic anticoagulation had more bleeding events and fewer thrombotic events than patients who received usual care.

Methods	Results	Limitations and Interpretation
INSPIRATION: Open-Label RCT of Intermediate-Dose Versus Prophylactic-Dose Anticoagulant in Patients in Intensive Care With COVID-19 in Iran[6]		

Key Inclusion Criteria:
• Admitted to ICU
• Hospitalized <7 days
Key Exclusion Criteria:
• Life expectancy <24 hours
• Indication for therapeutic anticoagulation
• Overt bleeding
Interventions:
• Intermediate-dose anticoagulation: enoxaparin 1 mg/kg daily (n = 276)
• Prophylactic-dose anticoagulation (n = 286)
Primary Endpoint:
• Composite of adjudicated acute VTE, ATE, ECMO, or all-cause mortality within 30 days
Key Secondary Endpoints:
• All-cause mortality
• VTE
• Bleeding event
	Participant Characteristics:
	• Median age 62 years; 58% men; median BMI 27
	• 44% with HTN; 28% with DM; 14% with coronary artery disease
	• 32% required NIV; 20% required MV
	• 23% on vasopressors; 93% on corticosteroids; 60% on RDV
	Primary Outcome:
	• Composite adjudicated acute VTE, ATE, ECMO, or all-cause mortality: 46% in therapeutic arm vs. 44% in prophylactic arm (OR 1.06; 95% CI, 0.76–1.48)
	Secondary Outcomes:
	• No difference between therapeutic and prophylactic arms:
	  • All-cause mortality: 43% vs. 41%
	  • VTE: 3% both arms
	  • Major bleeding and clinically relevant nonmajor bleeding: 6.3% vs. 3.1% (OR 2.02; 95% CI, 0.89–4.61)
		Key Limitations:
		• Open-label study
		• Not all patients received ICU-level care.
		Interpretation:
		• Intermediate-dose anticoagulation did not significantly reduce VTE and ATE, the need for ECMO, or mortality.
		• Although the difference was nonsignificant, patients who received intermediate-dose anticoagulation had more bleeding events than patients who received usual care.

Key: ATE = arterial thromboembolism; BMI = body mass index; CrCl = creatinine clearance; CVD = cardiovascular disease; DM = diabetes mellitus; ECMO = extracorporeal membrane oxygenation; HFNC = high-flow nasal cannula; HTN = hypertension; ICU = intensive care unit; LMWH = low-molecular-weight heparin; LOS = length of stay; MV = mechanical ventilation; NIV = noninvasive ventilation; the Panel = the COVID-19 Treatment Guidelines Panel; RCT = randomized controlled trial; RDV = remdesivir; SOC = standard of care; SpO_2 = oxygen saturation; UFH = unfractionated heparin; ULN = upper limit of normal; VTE = venous thromboembolism

References

1. ATTACC Investigators, ACTIV-4a Investigators, REMAP-CAP Investigators, et al. Therapeutic anticoagulation with heparin in noncritically ill patients with COVID-19. *N Engl J Med*. 2021;385(9):790-802. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34351721.
2. Sholzberg M, Tang GH, Rahhal H, et al. Effectiveness of therapeutic heparin versus prophylactic heparin on death, mechanical ventilation, or intensive care unit admission in moderately ill patients with COVID-19 admitted to hospital: RAPID randomised clinical trial. *BMJ*. 2021;375:n2400. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34649864.

3. Spyropoulos AC, Goldin M, Giannis D, et al. Efficacy and safety of therapeutic-dose heparin vs standard prophylactic or intermediate-dose heparins for thromboprophylaxis in high-risk hospitalized patients with COVID-19: the HEP-COVID randomized clinical trial. *JAMA Intern Med*. 2021;181(12):1612-1620. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34617959.
4. Lopes RD, de Barros ESPGM, Furtado RHM, et al. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. *Lancet*. 2021;397(10291):2253-2263. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34097856.
5. REMAP-CAP Investigators, ACTIV-4a Investigators, ATTACC Investigators, et al. Therapeutic anticoagulation with heparin in critically ill patients with COVID-19. *N Engl J Med*. 2021;385(9):777-789. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34351722.
6. INSPIRATION Investigators, Sadeghipour P, Talasaz AH, et al. Effect of intermediate-dose vs standard-dose prophylactic anticoagulation on thrombotic events, extracorporeal membrane oxygenation treatment, or mortality among patients with COVID-19 admitted to the intensive care unit: the INSPIRATION randomized clinical trial. *JAMA*. 2021;325(16):1620-1630. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33734299.

Supplements

Last Updated: February 11, 2021

Summary Recommendations
Vitamin C • There is insufficient evidence for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of vitamin C for the treatment of COVID-19. **Vitamin D** • There is insufficient evidence for the Panel to recommend either for or against the use of vitamin D for the treatment of COVID-19. **Zinc** • There is insufficient evidence for the Panel to recommend either for or against the use of zinc for the treatment of COVID-19. • The Panel **recommends against** using zinc supplementation above the recommended dietary allowance for the prevention of COVID-19, except in a clinical trial **(BIII)**.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional **Rating of Evidence:** I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

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

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

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

Vitamin C

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

Recommendation for Non-Critically Ill Patients With COVID-19

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

Rationale

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

Clinical Data on Vitamin C in Outpatients With COVID-19

Oral Ascorbic Acid Versus Zinc Gluconate Versus Both Agents Versus Standard of Care

In an open-label clinical trial that was conducted at two sites in the United States, outpatients with laboratory-confirmed SARS-CoV-2 infection were randomized to receive either 10 days of oral ascorbic acid 8,000 mg, zinc gluconate 50 mg, both agents, or standard of care.[3] The primary end point was the number of days required to reach a 50% reduction in the patient's symptom severity score. The study was stopped early by an operational and safety monitoring board due to futility after 40% of the planned 520 participants were enrolled (n = 214).

Patients who received standard of care achieved a 50% reduction in their symptom severity scores at a mean of 6.7 days (SD 4.4 days) compared with 5.5 days (SD 3.7 days) for the ascorbic acid arm, 5.9 days (SD 4.9 days) for the zinc gluconate arm, and 5.5 days (SD 3.4 days) for the arm that received both agents (overall $P = 0.45$). Nonserious adverse effects occurred more frequently in patients who received supplements than in those who did not; 39.5% of patients in the ascorbic acid arm, 18.5% in the zinc gluconate arm, and 32.1% in the arm that received both agents experienced nonserious adverse effects compared with 0% of patients in the standard of care arm (overall $P < 0.001$). The most common nonserious adverse effects in this study were gastrointestinal events.

The limitations of this study include the small sample size and the lack of a placebo control. In outpatients with COVID-19, treatment with high-dose zinc gluconate, ascorbic acid, or a combination of the two supplements did not significantly decrease the number of days required to reach a 50% reduction in a symptom severity score compared with standard of care.

Recommendation for Critically Ill Patients With COVID-19

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

Rationale

There are no controlled trials that have definitively demonstrated a clinical benefit for vitamin C in critically ill patients with COVID-19, and the available observational data are inconclusive. Studies of vitamin C regimens in sepsis patients and ARDS patients have reported variable efficacy and few safety concerns.

Clinical Data on Vitamin C in Critically Ill Patients

Intravenous Vitamin C Alone in Patients With COVID-19

A pilot clinical trial in China randomized 56 adults with COVID-19 in the intensive care unit to receive intravenous (IV) vitamin C 24 g per day or placebo for 7 days. The study was terminated early due to a reduction in the number of cases of COVID-19 in China. Overall, the study found no differences between the arms in mortality, the duration of mechanical ventilation, or the change in median sequential organ failure assessment (SOFA) scores. The study reported improvements in oxygenation (as measured by the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen [PaO_2/FiO_2]) from baseline to Day 7 in the treatment arm that were statistically greater than those observed in the placebo arm (+20.0 vs. -51.9; $P = 0.04$).[4]

Intravenous Vitamin C Alone in Patients Without COVID-19

A small, three-arm pilot study compared two regimens of IV vitamin C to placebo in 24 critically ill patients with sepsis. Over the 4-day study period, patients who received vitamin C 200 mg/kg per day and those who received vitamin C 50 mg/kg per day had lower SOFA scores and lower levels of proinflammatory markers than patients who received placebo.[5]

In a randomized controlled trial in critically ill patients with sepsis-induced ARDS (n = 167), patients who received IV vitamin C 200 mg/kg per day for 4 days had SOFA scores and levels of inflammatory markers that were similar to those observed in patients who received placebo. However, 28-day mortality was lower in the treatment group (29.8% vs. 46.3%; $P = 0.03$), coinciding with more days alive and free of the hospital and the intensive care unit.[6] A post hoc analysis of the study data reported a difference in median SOFA scores between the treatment group and placebo group at 96 hours; however, this difference was not present at baseline or 48 hours.[7]

Intravenous Vitamin C Plus Thiamine With or Without Hydrocortisone in Critically Ill Patients Without COVID-19

Two small studies that used historic controls reported favorable clinical outcomes (i.e., reduced mortality, reduced risk of progression to organ failure, and improved radiographic findings) in patients with sepsis or severe pneumonia who received a combination of vitamin C, thiamine, and hydrocortisone.[8,9] Subsequently, several randomized trials in which patients received vitamin C and thiamine (with or without hydrocortisone) to treat sepsis and septic shock showed that this combination conferred benefits for certain clinical parameters. However, no survival benefit was reported. Two trials observed reductions in organ dysfunction (as measured by change in SOFA score on Day 3)[10,11] or the duration of shock[12] without an effect on clinical outcomes. Three other trials, including a large trial of 501 sepsis patients, found no differences in any physiologic or outcome measures between the treatment and placebo groups.[13-15]

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

Other Considerations

It is important to note that high circulating concentrations of vitamin C may affect the accuracy of point-of-care glucometers.[16,17]

References

1. Wei XB, Wang ZH, Liao XL, et al. Efficacy of vitamin C in patients with sepsis: an updated meta-analysis. *Eur J Pharmacol*. 2020;868:172889. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31870831.
2. Fisher BJ, Seropian IM, Kraskauskas D, et al. Ascorbic acid attenuates lipopolysaccharide-induced acute lung injury. *Crit Care Med.* 2011;39(6):1454-1460. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21358394.
3. Thomas S, Patel D, Bittel B, et al. Effect of high-dose zinc and ascorbic acid supplementation vs usual care on symptom length and reduction among ambulatory patients with SARS-CoV-2 infection: the COVID A to Z randomized clinical trial. *JAMA Netw Open*. 2021;4(2):e210369. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33576820.
4. Zhang J, Rao X, Li Y, et al. Pilot trial of high-dose vitamin C in critically ill COVID-19 patients. *Ann Intensive Care*. 2021;11(1):5. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33420963.
5. Fowler AA, 3rd, Syed AA, Knowlson S, et al. Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. *J Transl Med*. 2014;12:32. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24484547.
6. Fowler AA, 3rd, Truwit JD, Hite RD, et al. Effect of vitamin C infusion on organ failure and biomarkers of inflammation and vascular injury in patients with sepsis and severe acute respiratory failure: the CITRIS-ALI randomized clinical trial. *JAMA*. 2019;322(13):1261-1270. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31573637.
7. Fowler AA, 3rd, Fisher BJ, Kashiouris MG. Vitamin C for sepsis and acute respiratory failure-reply. *JAMA*. 2020;323(8):792-793. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32096845.
8. Marik PE, Khangoora V, Rivera R, Hooper MH, Catravas J. Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock: a retrospective before-after study. *Chest*. 2017;151(6):1229-1238. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27940189.
9. Kim WY, Jo EJ, Eom JS, et al. Combined vitamin C, hydrocortisone, and thiamine therapy for patients with severe pneumonia who were admitted to the intensive care unit: propensity score-based analysis of a before-after cohort study. *J Crit Care*. 2018;47:211-218. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30029205.
10. Fujii T, Luethi N, Young PJ, et al. Effect of vitamin C, hydrocortisone, and thiamine vs hydrocortisone alone on time alive and free of vasopressor support among patients with septic shock: the VITAMINS randomized clinical trial. *JAMA*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31950979.
11. Chang P, Liao Y, Guan J, et al. Combined treatment with hydrocortisone, vitamin C, and thiamine for sepsis and septic shock: a randomized controlled trial. *Chest*. 2020;158(1):174-182. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32243943.
12. Iglesias J, Vassallo AV, Patel VV, Sullivan JB, Cavanaugh J, Elbaga Y. Outcomes of metabolic resuscitation using ascorbic acid, thiamine, and glucocorticoids in the early treatment of sepsis: the ORANGES trial. *Chest*. 2020;158(1):164-173. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32194058.
13. Hwang SY, Ryoo SM, Park JE, et al. Combination therapy of vitamin C and thiamine for septic shock: a multi-centre, double-blinded randomized, controlled study. *Intensive Care Med*. 2020;46(11):2015-2025. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32780166.
14. Moskowitz A, Huang DT, Hou PC, et al. Effect of ascorbic acid, corticosteroids, and thiamine on organ injury in septic shock: the ACTS randomized clinical trial. *JAMA*. 2020;324(7):642-650. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32809003.
15. Sevransky JE, Rothman RE, Hager DN, et al. Effect of vitamin C, thiamine, and hydrocortisone on ventilator- and vasopressor-free days in patients with sepsis: the VICTAS randomized clinical trial. *JAMA*. 2021;325(8):742-750. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33620405.
16. Hager DN, Martin GS, Sevransky JE, Hooper MH. Glucometry when using vitamin C in sepsis: a note of caution. *Chest*. 2018;154(1):228-229. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30044741.
17. Food and Drug Administration. Blood glucose monitoring devices. 2019. Available at: https://www.fda.gov/medical-devices/in-vitro-diagnostics/blood-glucose-monitoring-devices. Accessed March 26, 2021.

Vitamin D

Last Updated: April 21, 2021

Recommendation

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

Rationale

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

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

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

The rationale for using vitamin D is based largely on immunomodulatory effects that could potentially protect against COVID-19 infection or decrease the severity of illness. Ongoing observational studies are evaluating the role of vitamin D in preventing and treating COVID-19. Some investigational trials on the use of vitamin D in people with COVID-19 are being planned or are already accruing participants. These trials will administer vitamin D alone or in combination with other agents to participants with and without vitamin D deficiency. The latest information on these clinical trials can be found on ClinicalTrials.gov.

Clinical Data

Randomized Clinical Trial of Vitamin D Versus Placebo in Patients With Moderate to Severe COVID-19

In a double-blind, placebo-controlled randomized trial that was conducted at two sites in Brazil, 240 hospitalized patients with moderate to severe COVID-19 received either a single dose of 200,000 international units of vitamin D_3 or placebo.[10] Moderate to severe COVID-19 was defined as patients with a positive result on a SARS-CoV-2 polymerase chain reaction test (or compatible computed tomography scan findings) and a respiratory rate >24 breaths/min, oxygen saturation <93% on room air, or risk factors for complications. The primary outcome in this study was the length of the hospital stay.

The median length of stay was not significantly different between the vitamin D_3 arm (7.0 days [IQR 4.0–10.0 days]) and the placebo arm (7.0 days [IQR 5.0–13.0 days]; $P = 0.59$, log-rank test). No significant differences were observed between the arms in the percentages of patients who were admitted to the intensive care unit, who required mechanical ventilation, or who died during hospitalization.

It should be noted that this study had a small sample size and enrolled participants with a variety of comorbidities and concomitant medications. The time between symptom onset and randomization was relatively long, with patients randomized at a mean of 10.3 days after symptom onset. In this study, a single, high dose of vitamin D_3 did not significantly reduce the length of stay for hospitalized patients with COVID-19.

References

1. Aranow C. Vitamin D and the immune system. *J Investig Med*. 2011;59(6):881-886. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21527855.
2. Forrest KY, Stuhldreher WL. Prevalence and correlates of vitamin D deficiency in US adults. *Nutr Res*. 2011;31(1):48-54. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21310306.
3. Lu D, Zhang J, Ma C, et al. Link between community-acquired pneumonia and vitamin D levels in older patients. *Z Gerontol Geriatr*. 2018;51(4):435-439. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28477055.
4. Science M, Maguire JL, Russell ML, Smieja M, Walter SD, Loeb M. Low serum 25-hydroxyvitamin D level and risk of upper respiratory tract infection in children and adolescents. *Clin Infect Dis*. 2013;57(3):392-397. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23677871.
5. Fisher SA, Rahimzadeh M, Brierley C, et al. The role of vitamin D in increasing circulating T regulatory cell numbers and modulating T regulatory cell phenotypes in patients with inflammatory disease or in healthy volunteers: a systematic review. *PLoS One*. 2019;14(9):e0222313. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31550254.
6. Martineau AR, Jolliffe DA, Hooper RL, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. *BMJ*. 2017;356:i6583. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28202713.
7. Amrein K, Schnedl C, Holl A, et al. Effect of high-dose vitamin D3 on hospital length of stay in critically ill patients with vitamin D deficiency: the VITdAL-ICU randomized clinical trial. *JAMA*. 2014;312(15):1520-1530. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25268295.
8. National Heart, Lung, and Blood Institute PETAL Clinical Trials Network, Ginde AA, et al. Early high-dose vitamin D3 for critically ill, vitamin D-deficient patients. *N Engl J Med*. 2019;381(26):2529-2540. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31826336.
9. Institute of Medicine. Dietary Reference Intakes for Calcium and Vitamin D. The National Academies Press; 2011.
10. Murai IH, Fernandes AL, Sales LP. Effect of a single high dose of vitamin D3 on hospital length of stay in patients with moderate to severe COVID-19: a randomized clinical trial. 2021; Published online ahead of print. Available at: https://pubmed.ncbi.nlm.nih.gov/33595634/.

Zinc

Last Updated: April 21, 2021

Recommendations

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

Rationale

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

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

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

Clinical Data

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

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

Results

- There were no significant differences between the two arms in the percentages of patients who recovered within 28 days (79.2% in the hydroxychloroquine plus zinc arm vs. 77.9% in the hydroxychloroquine only arm; $P = 0.969$), the need for mechanical ventilation ($P = 0.537$), or

overall mortality ($P = 0.986$).

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

Limitations

- This study had a relatively small sample size.

Interpretation

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

Open-Label, Randomized Trial of Zinc Versus Ascorbic Acid Versus Zinc Plus Ascorbic Acid Versus Standard of Care in Outpatients With COVID-19

In an open-label clinical trial that was conducted at two sites in the United States, outpatients with laboratory-confirmed SARS-CoV-2 infection were randomized to receive either 10 days of zinc gluconate 50 mg, ascorbic acid 8,000 mg, both agents, or standard of care. The primary end point was the number of days required to reach a 50% reduction in the patient's symptom severity score. The study was stopped early by an operational and safety monitoring board due to futility after 40% of the planned 520 participants were enrolled (n = 214).[9]

Results

- Participants who received standard of care achieved a 50% reduction in their symptom severity scores at a mean of 6.7 days (SD 4.4 days) compared with 5.5 days (SD 3.7 days) for the ascorbic acid arm, 5.9 days (SD 4.9 days) for the zinc gluconate arm, and 5.5 days (SD 3.4 days) for the arm that received both agents (overall $P = 0.45$).
- Nonserious adverse effects occurred more frequently in patients who received supplements than in those who did not; 39.5% of patients in the ascorbic acid arm, 18.5% in the zinc gluconate arm, and 32.1% in the arm that received both agents experienced nonserious adverse effects compared with 0% of patients in the standard of care arm (overall $P < 0.001$). The most common nonserious adverse effects in this study were gastrointestinal events.

Limitations

- The study had a small sample size.
- There was no placebo control.

Interpretation

In outpatients with COVID-19, treatment with high-dose zinc gluconate, ascorbic acid, or a combination of the two supplements did not significantly decrease the number of days required to reach a 50% reduction in a symptom severity score compared with standard of care.

Observational Study of Zinc Supplementation in Hospitalized Patients

A retrospective study enrolled 242 patients with polymerase chain reaction-confirmed SARS-CoV-2 infection who were admitted to Hoboken University Medical Center. One hundred and ninety-six patients (81.0%) received a total daily dose of zinc sulfate 440 mg (100 mg of elemental zinc); of those, 191 patients (97%) also received hydroxychloroquine. Among the 46 patients who did not receive zinc, 32 patients (70%) received hydroxychloroquine. The primary outcome was days from hospital admission to in-hospital mortality, and the primary analysis explored the causal association between zinc therapy and survival.[10]

Results

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

Limitations

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

Interpretation

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

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

This study has not been peer reviewed.

This multicenter, retrospective cohort study of hospitalized adults with SARS-CoV-2 infection who were admitted to four New York City hospitals between March 10 and May 20, 2020, compared patients who received zinc plus hydroxychloroquine to those who received treatment that did not include this combination.[11]

Results

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

Limitations

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

Interpretation

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

References

1. te Velthuis AJ, van den Worm SH, Sims AC, Baric RS, Snijder EJ, van Hemert MJ. Zn(2+) inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. *PLoS Pathog*. 2010;6(11):e1001176. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21079686.
2. Xue J, Moyer A, Peng B, Wu J, Hannafon BN, Ding WQ. Chloroquine is a zinc ionophore. *PLoS One*. 2014;9(10):e109180. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25271834.
3. Calder PC, Carr AC, Gombart AF, Eggersdorfer M. Optimal nutritional status for a well-functioning immune system is an important factor to protect against viral infections. *Nutrients*. 2020;12(4). Available at: https://www.ncbi.nlm.nih.gov/pubmed/32340216.
4. Hambridge K. The management of lipohypertrophy in diabetes care. *Br J Nurs*. 2007;16(9):520-524. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17551441.
5. National Institutes of Health. Office of Dietary Supplements. Zinc fact sheet for health professionals. 2020. Available at: https://ods.od.nih.gov/factsheets/Zinc-HealthProfessional/.
6. Myint ZW, Oo TH, Thein KZ, Tun AM, Saeed H. Copper deficiency anemia: review article. *Ann Hematol*. 2018;97(9):1527-1534. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29959467.
7. Kumar N. Copper deficiency myelopathy (human swayback). *Mayo Clin Proc*. 2006;81(10):1371-1384. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17036563.
8. Abd-Elsalam S, Soliman S, Esmail ES, et al. Do zinc supplements enhance the clinical efficacy of hydroxychloroquine?: a randomized, multicenter trial. *Biol Trace Elem Res*. 2020;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33247380.
9. Thomas S, Patel D, Bittel B. Effect of high-dose zinc and ascorbic acid supplementation vs usual care on symptom length and reduction among ambulatory patients with SARS-CoV-2 Infection: the COVID a to z randomized clinical trial. *JAMA Netw Open*. 2021;4(2):e210369. Available at: https://pubmed.ncbi.nlm.nih.gov/33576820/.
10. Yao JS, Paguio JA, Dee EC, et al. The minimal effect of zinc on the survival of hospitalized patients with COVID-19: an observational study. *Chest*. 2021;159(1):108-111. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32710890.
11. Frontera JA, Rahimian JO, Yaghi S, et al. Treatment with zinc is associated with reduced in-hospital mortality among COVID-19 patients: a multi-center cohort study. *Res Sq*. 2020;Preprint. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33140042.

Considerations for Using Concomitant Medications in Patients With COVID-19

Last Updated: December 16, 2021

Summary Recommendations
• Patients with COVID-19 who are receiving concomitant medications (e.g., angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], HMG-CoA reductase inhibitors [statins], systemic or inhaled corticosteroids, nonsteroidal anti-inflammatory drugs, acid-suppressive therapy) for underlying medical conditions **should not discontinue** these medications during acute management of COVID-19 unless discontinuation is otherwise warranted by their clinical condition (**AIIa** for **ACE inhibitors and ARBs**; **AIII** for **other medications**). • The COVID-19 Treatment Guidelines Panel **recommends against** using medications off-label to treat COVID-19 if they have not been shown to be safe and effective for this indication in a clinical trial **(AIII)**.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional **Rating of Evidence:** I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

Individuals with underlying medical conditions, such as cardiovascular disease, pulmonary disease, diabetes, and malignancy, 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.

References

1. Patel AB, Verma A. COVID-19 and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: what is the evidence? *JAMA*. 2020;323(18):1769-1770. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32208485.
2. Lee KCH, Sewa DW, Phua GC. Potential role of statins in COVID-19. *Int J Infect Dis*. 2020;96:615-617. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32502659.
3. Kashour T, Halwani R, Arabi YM, et al. Statins as an adjunctive therapy for COVID-19: the biological and clinical plausibility. *Immunopharmacol Immunotoxicol*. 2021;43(1):37-50. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33406943.
4. Mather JF, Seip RL, McKay RG. Impact of famotidine use on clinical outcomes of hospitalized patients with COVID-19. *Am J Gastroenterol*. 2020;115(10):1617-1623. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32852338.
5. Yousefifard M, Zali A, Zarghi A, Madani Neishaboori A, Hosseini M, Safari S. Non-steroidal anti-inflammatory drugs in management of COVID-19; a systematic review on current evidence. *Int J Clin Pract*. 2020;74(9):e13557. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32460369.
6. Lopes RD, Macedo AVS, de Barros E Silva PGM, et al. Effect of discontinuing vs continuing angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on days alive and out of the hospital in patients admitted with COVID-19: a randomized clinical trial. *JAMA*. 2021;325(3):254-264. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33464336.
7. Cohen JB, Hanff TC, William P, et al. Continuation versus discontinuation of renin-angiotensin system inhibitors in patients admitted to hospital with COVID-19: a prospective, randomised, open-label trial. *Lancet Respir Med*. 2021;9(3):275-284. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33422263.
8. Bauer A, Schreinlechner M, Sappler N, et al. Discontinuation versus continuation of renin-angiotensin-system inhibitors in COVID-19 (ACEI-COVID): a prospective, parallel group, randomised, controlled, open-label trial. *Lancet Respir Med*. 2021;9(8):863-872. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34126053.
9. Food and Drug Administration. FDA advises patients on use of non-steroidal anti-inflammatory drugs (NSAIDs) for COVID-19. 2020. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-patients-use-non-steroidal-anti-inflammatory-drugs-nsaids-covid-19. Accessed October 26, 2021.
10. Bozkurt B, Kovacs R, Harrington B. Joint HFSA/ACC/AHA statement addresses concerns re: using RAAS antagonists in COVID-19. *J Card Fail*. 2020;26(5):370. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32439095.
11. Cazzola M, Ora J, Bianco A, Rogliani P, Matera MG. Guidance on nebulization during the current COVID-19 pandemic. *Respir Med*. 2021;176:106236. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33248363.
12. Sethi S, Barjaktarevic IZ, Tashkin DP. The use of nebulized pharmacotherapies during the COVID-19 pandemic. *Ther Adv Respir Dis*. 2020;14:1753466620954366. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33167796.
13. University of Liverpool. COVID-19 drug interactions. 2021. Available at: https://www.covid19-druginteractions.org/. Accessed November 1, 2021.

COVID-19 and Special Populations

Last Updated: October 9, 2020

Key Considerations

There is current guidance from the Centers for Disease Control and Prevention (CDC), the American College of Obstetricians and Gynecologists (ACOG), and the Society for Maternal-Fetal Medicine (SMFM) on the management of pregnant patients with COVID-19.[1-4] This section of the COVID-19 Treatment Guidelines complements that guidance. Below are key considerations regarding the management of COVID-19 in pregnancy.
• Pregnant women should be counseled about the potential for severe disease from SARS-CoV-2 infection and the recommended measures to take to protect themselves and their families from infection.
• If hospitalization for COVID-19 is indicated in a pregnant woman, care should be provided in a facility that can conduct maternal and fetal monitoring, when appropriate.
• Management of COVID-19 in the pregnant patient should include:
  • Fetal and uterine contraction monitoring, when appropriate, based on gestational age
  • Individualized delivery planning
  • A multispecialty, team-based approach that may include consultation with obstetric, maternal-fetal medicine, infectious disease, pulmonary and critical care, and pediatric specialists, as appropriate
• The COVID-19 Treatment Guidelines Panel (the Panel) recommends that potentially effective treatment for COVID-19 should not be withheld from pregnant women because of theoretical concerns related to the safety of therapeutic agents in pregnancy **(AIII)**.
• Decisions regarding the use of drugs approved for other indications or investigational drugs for the treatment of COVID-19 in pregnant patients must be made with shared decision-making between the patient and the clinical team, considering the safety of the medication for the pregnant woman and the fetus and the severity of maternal disease. For detailed guidance on the use of COVID-19 therapeutic agents in pregnancy, please refer to the pregnancy considerations subsection of each individual section of the Guidelines.

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

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

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

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

Special Considerations in Pregnancy

Last Updated: July 8, 2021

Key Considerations

There is current guidance from the Centers for Disease Control and Prevention, the American College of Obstetricians and Gynecologists, and the Society for Maternal-Fetal Medicine on the management of pregnant patients with COVID-19. This section of the COVID-19 Treatment Guidelines complements that guidance. The following are key considerations regarding the management of COVID-19 in pregnancy:
• Pregnant people should be counseled about the increased risk for severe disease from SARS-CoV-2 infection and receive recommendations on ways to protect themselves and their families from infection.
• If hospitalization for COVID-19 is indicated for a pregnant patient, care should be provided in a facility that can conduct maternal and fetal monitoring, when appropriate.
• Management of COVID-19 in pregnant patients should include:
  • Fetal and uterine contraction monitoring based on gestational age, when appropriate
  • Individualized delivery planning
  • A multispecialty, team-based approach that may include consultation with obstetric, maternal-fetal medicine, infectious disease, pulmonary-critical care, and pediatric specialists, as appropriate
  • In general, the therapeutic management of pregnant patients with COVID-19 should be the same as for nonpregnant patients. The COVID-19 Treatment Guidelines Panel **recommends against** withholding treatment for COVID-19 and SARS-CoV-2 vaccination from pregnant or lactating individuals because of theoretical safety concerns **(AIII)**. For details regarding therapeutic recommendations and pregnancy considerations, see General Management of Nonhospitalized Patients With Acute COVID-19 and the individual drug sections.
• Pregnant or lactating patients with COVID-19 and their clinical teams should discuss the use of investigational drugs or drugs that are approved for other indications as treatments for COVID-19. During this shared decision-making process, the patient and the clinical team should consider the safety of the medication for the pregnant or lactating individual and the fetus and the severity of maternal disease. For detailed guidance on using COVID-19 therapeutic agents during pregnancy, please refer to the pregnancy considerations subsections found in the Antiviral Therapy and Immunomodulators sections of these Guidelines.
• The decision to feed the infant breast milk while the patient is receiving therapeutic agents for COVID-19 should be a collaborative effort between the patient and the clinical team, including infant care providers. The patient and the clinical team should discuss the potential benefits of the therapeutic agent and evaluate the potential impact of pausing lactation on the future of breast milk delivery to the infant.

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

Epidemiology of COVID-19 in Pregnancy

Early in the pandemic, reports of COVID-19 disease acquired during pregnancy were limited to case series or studies that did not compare pregnant patients to age-matched, nonpregnant controls, and these reports were largely reassuring. Subsequent data have indicated that while the overall risk of severe illness is low, COVID-19 is associated with more severe disease in pregnant people than in nonpregnant people.[1] There is also an increased risk of poor obstetric outcomes among pregnant people with COVID-19, such as preterm birth.[2,3]

In November 2020, the Centers for Disease Control and Prevention (CDC) released surveillance data on outcomes in approximately 400,000 reproductive-aged women with symptomatic, laboratory-confirmed COVID-19.[1] After adjusting for age, race/ethnicity, and underlying medical conditions, pregnant women

had significantly higher rates of intensive care unit (ICU) admission (10.5 vs. 3.9 cases per 1,000 cases; adjusted risk ratio [aRR] 3.0; 95% CI, 2.6–3.4), mechanical ventilation (2.9 vs. 1.1 cases per 1,000 cases; aRR 2.9; 95% CI, 2.2–3.8), extracorporeal membrane oxygenation (0.7 vs. 0.3 cases per 1,000 cases; aRR 2.4; 95% CI, 1.5–4.0), and death (1.5 vs. 1.2 cases per 1,000 cases; aRR 1.7; 95% CI, 1.2–2.4). The increased risk for severe disease was most significant in women aged 35 to 44 years, who were almost four times as likely to be mechanically ventilated and twice as likely to die as nonpregnant women of the same age.

Notably, among Hispanic women, pregnancy was associated with a risk of death that was 2.4 times higher (95% CI, 1.3–4.3) than the risk observed in nonpregnant Hispanic women. Racial and ethnic disparities were also seen in other reports. Among 8,207 pregnant women with COVID-19 who were reported to CDC, the proportion of those who were reported to be Hispanic (46%) and Black (22%) was higher than the proportion of Hispanic and Black women who gave birth in 2019 (24% and 15%, respectively), suggesting that pregnant people who are Hispanic or Black may be disproportionately affected by SARS-CoV-2 infection.[4]

In an ongoing systematic review that includes 192 studies to date, maternal factors that were associated with severe disease included increased maternal age (OR 1.83; 95% CI, 1.27–2.63; 3,561 women from 7 studies); a high body mass index (OR 2.37; 95% CI, 1.83–3.07; 3,367 women from 5 studies); any pre-existing maternal comorbidity, including chronic hypertension and diabetes (OR 1.81; 95% CI, 1.49–2.20; 2,634 women from 3 studies); pre-eclampsia (OR 4.21; 95% CI, 1.27–14.0; 274 women from 4 studies); and pre-existing diabetes (OR 2.12; 95% CI, 1.62–2.78; 3,333 women from 3 studies).[5] Compared with pregnant women and recently pregnant women without COVID-19, pregnant women with COVID-19 were at a higher risk of any instance of preterm birth (OR 1.47; 95% CI, 1.14–1.91; 8,549 women from 18 studies) and stillbirth (OR 2.84; 95% CI, 1.25–6.45; 5,794 women from 9 studies).

An observational cohort study of all pregnant patients at 33 U.S. hospitals with a singleton gestation and a positive result on a SARS-CoV-2 virologic test evaluated maternal characteristics and outcomes across disease severity.[6] The data suggested that adverse perinatal outcomes were more common in patients with severe or critical disease than in asymptomatic patients with SARS-CoV-2 infection, including an increased incidence of cesarean delivery (59.6% vs. 34.0% of patients; aRR 1.57; 95% CI, 1.30–1.90), hypertensive disorders of pregnancy (40.4% vs. 18.8%; aRR 1.61; 95% CI, 1.18–2.20), and preterm birth (41.8% vs. 11.9%; aRR 3.53; 95% CI, 2.42–5.14). The perinatal outcomes for those with mild to moderate illness were similar to those observed among asymptomatic patients with SARS-CoV-2 infection.

Although vertical transmission of SARS-CoV-2 is possible, current data suggest that it is rare.[7] A review of 101 infants born to 100 women with SARS-CoV-2 infection at a single U.S. academic medical center found that 2 infants (2%) had indeterminate SARS-CoV-2 polymerase chain reaction (PCR) results, which were presumed to be positive; however, the infants exhibited no evidence of clinical disease. It is reassuring that the majority of the infants received negative PCR results after rooming with their mothers and breastfeeding directly (the mothers in this study practiced appropriate hand and breast hygiene).

Managing COVID-19 in Pregnancy

Pregnant people should be counseled about the increased risk for severe disease from SARS-CoV-2 and the measures they can take to protect themselves and their families from infection. These measures include practicing physical distancing, washing their hands regularly, and wearing a face covering (if indicated). If the patient is not vaccinated, they should be counseled about wearing a face covering and getting vaccinated against SARS-CoV-2 infection. CDC, the American College of Obstetricians and Gynecologists (ACOG), and the Society for Maternal-Fetal Medicine highlight the importance of accessing prenatal care. ACOG provides a list of frequently asked questions on using telehealth to

deliver antenatal care, when appropriate.

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

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

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

In general, the recommendations for managing COVID-19 in nonpregnant patients also apply to pregnant patients.

Therapeutic Management of COVID-19 in the Setting of Pregnancy

Potentially effective treatments for COVID-19 should not be withheld from pregnant people because of theoretical concerns related to the safety of using those therapeutic agents in pregnancy **(AIII)**.

Pregnant or lactating patients with COVID-19 and their clinical teams should discuss the use of investigational drugs or drugs that are approved for other indications as treatments for COVID-19. During this shared decision-making process, the patient and the clinical team should consider the safety of the medication for the pregnant or lactating individual and the fetus and the severity of maternal disease. For detailed guidance on the use of COVID-19 therapeutic agents during pregnancy, please refer to the pregnancy considerations subsections found in the Antiviral Therapy and Immunomodulators sections of these Guidelines.

The use of anti-SARS-CoV-2 monoclonal antibodies can be considered in pregnant people with COVID-19, especially in those who have additional risk factors for severe disease. There is no pregnancy-specific data on the use of monoclonal antibodies; however, other immunoglobulin G products have been safely used in pregnancy when their use is indicated. Therefore, these products should not be withheld in the setting of pregnancy.

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

Timing of Delivery

ACOG provides detailed guidance on the timing of delivery and the risk of vertical transmission of SARS-CoV-2.

In most cases, the timing of delivery should be dictated by obstetric indications rather than maternal diagnosis of COVID-19. For women who had suspected or confirmed COVID-19 early in pregnancy who recover, no alteration to the usual timing of delivery is indicated.

Post-Delivery

The majority of studies have not demonstrated the presence of SARS-CoV-2 in breast milk; therefore, breastfeeding is not contraindicated for people with laboratory-confirmed or suspected SARS-CoV-2 infection.[8] Precautions should be taken to avoid transmission to the infant, including practicing good hand hygiene, wearing face coverings, and performing proper pump cleaning before and after breast milk expression.

The decision to feed the infant breast milk while the patient is receiving therapeutic agents for COVID-19 should be a joint effort between the patient and the clinical team, including infant care providers. The patient and the clinical team should discuss the potential benefits of the therapeutic agent and evaluate the potential impact of pausing lactation on the future of breast milk delivery to the infant.

Specific guidance on the post-delivery management of infants born to mothers with known or suspected SARS-CoV-2 infection, including breastfeeding recommendations, is provided by CDC and the American Academy of Pediatrics, as well as the Special Considerations in Children section in these Guidelines.

SARS-CoV-2 Vaccine in Pregnancy

A study that used data from three vaccine safety reporting systems in the United States reported that the frequency of adverse events among 35,691 vaccine recipients who identified as pregnant was similar to the frequency observed among nonpregnant patients. Local injection site pain, nausea, and vomiting were reported slightly more frequently in pregnant people than in nonpregnant people. Other systemic reactions were reported more frequently among nonpregnant vaccine recipients, but the overall reactogenicity profile was similar for pregnant and nonpregnant patients. Surveillance data from 3,958 pregnant patients who were enrolled in CDC's v-safe Vaccine Pregnancy Registry showed that, among 827 people who completed their pregnancies, there were no obvious safety signals among obstetric or neonatal outcomes when rates of pregnancy loss (spontaneous abortion or stillbirth), preterm birth, congenital anomalies, infants who were small for gestational age, and neonatal death were compared to historic incidences in the peer-reviewed literature.[9] ACOG has published practice guidance on using COVID-19 vaccines in pregnant and lactating people, including a guide to assist clinicians during risk and benefit conversations with pregnant patients.

References

1. Zambrano LD, Ellington S, Strid P, et al. Update: characteristics of symptomatic women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status—United States, January 22–October 3, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(44):1641-1647. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33151921.
2. Ko JY, DeSisto CL, Simeone RM, et al. Adverse pregnancy outcomes, maternal complications, and severe illness among U.S. delivery hospitalizations with and without a COVID-19 diagnosis. *Clin Infect Dis*. 2021;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33977298.
3. Woodworth KR, Olsen EO, Neelam V, et al. Birth and infant outcomes following laboratory-confirmed SARS-CoV-2 infection in pregnancy—SET-NET, 16 jurisdictions, March 29–October 14, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(44):1635-1640. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33151917.
4. Ellington S, Strid P, Tong VT, et al. Characteristics of women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status—United States, January 22–June 7, 2020. *MMWR Morb Mortal*

Wkly Rep. 2020;69(25):769-775. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32584795.

5. Allotey J, Stallings E, Bonet M, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. *BMJ*. 2020;370:m3320. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32873575.
6. Metz TD, Clifton RG, Hughes BL, et al. Disease severity and perinatal outcomes of pregnant patients with coronavirus disease 2019 (COVID-19). *Obstet Gynecol*. 2021;137(4):571-580. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33560778.
7. Dumitriu D, Emeruwa UN, Hanft E, et al. Outcomes of neonates born to mothers with severe acute respiratory syndrome coronavirus 2 infection at a large medical center in New York City. *JAMA Pediatr*. 2021;175(2):157-167. Available at: https://pubmed.ncbi.nlm.nih.gov/33044493/.
8. The American College of Obstetricians and Gynecologists. COVID-19 FAQs for obstetrician-gynecologists, obstetrics. 2020. Available at: https://www.acog.org/clinical-information/physician-faqs/covid-19-faqs-for-ob-gyns-obstetrics. Accessed February 8, 2021.
9. Shimabukuro TT, Kim SY, Myers TR, et al. Preliminary findings of mRNA COVID-19 vaccine safety in pregnant persons. *N Engl J Med*. 2021;384(24):2273-2282. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33882218.

Special Considerations in Children

Last Updated: February 24, 2022

Summary Recommendations

General Considerations
• SARS-CoV-2 infection is generally milder in children than in adults, and a substantial proportion of children with the disease have asymptomatic infection.
• Most children with SARS-CoV-2 infection will not require any specific therapy.
• Children who have a history of medical complexity (e.g., due to neurologic impairment, developmental delays, or genetic syndromes, including trisomy 21), obesity, chronic cardiopulmonary disease, or who are immunocompromised, as well as non-White children and older teenagers may be at increased risk for severe disease.
• There are limited data on the pathogenesis and clinical spectrum of COVID-19 disease in children. There are no pediatric data from placebo-controlled randomized clinical trials and limited data from observational studies to inform the development of pediatric-specific recommendations for the treatment of COVID-19.
 	
Specific Therapy for Children
• In the absence of adequate data on the treatment of children with acute COVID-19, recommendations are based on outcome and safety data for adult patients and the child's risk of disease progression.
• Most children with mild or moderate disease can be managed with supportive care alone **(AIII)**.
• **Remdesivir** is recommended for:
  • Hospitalized children aged ≥12 years with COVID-19 who have risk factors for severe disease and have an emergent or increasing need for supplemental oxygen **(BIII)**.
  • Hospitalized children aged ≥16 years with COVID-19 who have an emergent or increasing need for supplemental oxygen regardless of whether they have risks factors for severe disease **(BIII)**.
• In consultation with a pediatric infectious disease specialist, **remdesivir** can be considered for hospitalized children of all ages with COVID-19 who have an emergent or increasing need for supplemental oxygen **(CIII)**.
• The COVID-19 Treatment Guidelines Panel (the Panel) recommends using **dexamethasone** for hospitalized children with COVID-19 who require high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation **(BIII)**.
• There is insufficient pediatric evidence for the Panel to recommend either for or against the use of anti-SARS-CoV-2 monoclonal antibody products for children with COVID-19 who are not hospitalized but who have risk factors for severe disease. Based on adult studies, bamlanivimab plus etesevimab or casirivimab plus imdevimab may be considered on a case-by-case basis for nonhospitalized children who meet Emergency Use Authorization (EUA) criteria for high-risk of severe disease, especially those who meet more than 1 criterion or are aged ≥16 years. The Panel recommends consulting a pediatric infectious disease specialist in such cases.
• The Panel **recommends against** the use of **convalescent plasma** for hospitalized children with COVID-19 who do not require mechanical ventilation, except in a clinical trial **(AIII)**. The Panel **recommends against** the use of **convalescent plasma** for pediatric patients with COVID-19 who are mechanically ventilated **(AIII)**. In consultation with a pediatric infectious disease specialist, high-titer convalescent plasma may be considered on a case-by-case basis for hospitalized children who meet the EUA criteria for its use.
• There is insufficient evidence for the Panel to recommend either for or against the use of baricitinib in combination with remdesivir for the treatment of COVID-19 in hospitalized children in whom corticosteroids cannot be used.
• There is insufficient evidence for the Panel to recommend either for or against the use of tocilizumab in hospitalized children with COVID-19 or multisystem inflammatory syndrome in children (MIS-C). The Panel **recommends against** the use of **sarilumab** for hospitalized children with COVID-19 or MIS-C, except in a clinical trial **(AIII)**.
• MIS-C is a serious delayed complication of SARS-CoV-2 infection that may develop in a minority of children and young adults. See Therapeutic Management of Hospitalized Pediatric Patients With Multisystem Inflammatory Syndrome in Children (MIS-C) (With Discussion on Multisystem Inflammatory Syndrome in Adults [MIS-A]) for the Panel's recommendations for treating children with MIS-C.

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

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

Epidemiology

Data from the Centers for Disease Control and Prevention (CDC) demonstrate a lower incidence of SARS-CoV-2 infection and severe disease in children than in adults.[1] However, without more systematic testing for children (including for children with mild symptoms as part of contact tracing) or seroprevalence studies, the true burden of pediatric SARS-CoV-2 infection remains unclear. Data on the pathogenesis and disease severity of SARS-CoV-2 infection in children are increasing but are still limited compared to the data in adults. Several large epidemiologic studies suggest that severe manifestations of acute disease are substantially less common in children than in adults. Although only a small percentage of children with COVID-19 will require medical attention, intensive care unit (ICU)-admission rates for hospitalized children are comparable to those for hospitalized adults with COVID-19.[2-10]

Clinical Manifestations

The signs and symptoms of SARS-CoV-2 infection in children may be similar to those in adults, but most children may be asymptomatic or only have a few symptoms. The most common signs and symptoms of COVID-19 in hospitalized children are fever, nausea/vomiting, cough, shortness of breath, and upper respiratory symptoms.[9,11] Of note, signs and symptoms of COVID-19 may overlap significantly with those of other viral infections, including influenza and other respiratory and enteric viral infections. Although the true incidence of asymptomatic SARS-CoV-2 infection is unknown, asymptomatic infection was reported in up to 45% of children who underwent surveillance testing at the time of hospitalization for a non-COVID-19 indication.[12]

SARS-CoV-2 has been associated with a potentially severe inflammatory syndrome in children and young adults (multisystem inflammatory syndrome in children [MIS-C]), which is discussed below.

Risk Factors

Data to clearly establish risk factors for severe COVID-19 in children are limited. Data reported to CDC show lower hospitalization rates and ICU admission rates for children with COVID-19 than for adults with the disease.[11,13] COVID-19-related hospitalization rates for children were highest in children aged <2 years and higher in Hispanic and Black children than in White children. The majority of hospitalized children with acute COVID-19 had underlying conditions, with obesity, chronic lung disease, and prematurity (data collected only for children aged <2 years) being the most prevalent.[14] Risk factors such as obesity may be more applicable to older teenagers.

In a large study of hospitalized children from the United Kingdom, age <1 month, age 10 to 14 years, and Black race were associated with admission to critical care units in a multivariate analysis.[9] Another large, multicenter study from Europe identified male sex, pre-existing medical conditions, and the presence of lower respiratory tract disease at presentation as additional risk factors for ICU admission in multivariable models.[10]

Deaths associated with COVID-19 among those aged <21 years are higher among children aged 10 to 20 years, especially young adults aged 18 to 20 years, as well as among Hispanic, Black, and American Indian/Alaska Native persons.[15] A high proportion of the fatal cases of pediatric COVID-19 are in children with underlying medical conditions, most commonly chronic lung disease, obesity, and neurological and developmental disorders.

Based on data for adults with COVID-19 and extrapolations from data for non-COVID-19 pediatric respiratory viral infections, severely immunocompromised children and those with underlying cardiopulmonary disease may be at higher risk for severe COVID-19. Initial reports of SARS-CoV-2 infection among pediatric patients with cancer and pediatric solid organ transplant recipients have demonstrated a low frequency of infection and associated morbidity;[16-20] however, similar reports for other immunocompromised pediatric populations are limited.[21] A few reports have demonstrated a higher prevalence of asthma in pediatric COVID-19 cases, although the association between asthma and severe disease is not clearly defined.[7,8] Congenital heart disease may be associated with an increased risk of severe COVID-19, but the condition has not been consistently identified as a risk factor.[22,23] Guidance on the treatment of COVID-19 in children endorsed by the Pediatric Infectious Diseases Society specifies additional risk factors to consider when making decisions about antiviral and monoclonal antibody (mAb) therapy for pediatric patients.[24,25]

Persistent symptoms after acute COVID-19 have been described in adults, although the incidence of this sequelae in children remains unknown and is an active area of research (see Clinical Spectrum of SARS-CoV-2 Infection). Cardiac imaging studies have described myocardial injury in young athletes who had only mild disease;[26] additional studies are needed to determine long-term cardiac sequelae.

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

Vertical transmission of SARS-CoV-2 is thought to be rare, but suspected or probable vertical transmission has been described.[27-29] Initial data on perinatal transmission of SARS-CoV-2 were limited to small case series with conflicting results; some studies demonstrated lack of transmission, whereas others were not able to definitively rule out this possibility.[30-33] Among 100 women with SARS-CoV-2 infection who delivered 101 infants, only 2 infants had equivocal reverse transcription polymerase chain reaction (RT-PCR) results that may have reflected SARS-CoV-2 infection, even though most of the infants remained with their mothers, in rooms with infection prevention measures in place, and were breast fed.[34]

Infants born to individuals with SARS-CoV-2 infection may have higher risk of poor clinical outcomes than those born to individuals without SARS-CoV-2 infection, although data are conflicting. In a systematic review of case series in pregnant women with confirmed SARS-CoV-2 infection (predominantly from China), the preterm birth rate was 20.1% (57 of 284 births were preterm; 95% CI, 15.8–25.1), the cesarean delivery rate was 84.7% (33 of 392 births were by cesarean delivery; 95% CI, 80.8–87.9), there was no vertical transmission, and the neonatal death rate was 0.3% (1 of 313 neonates died; 95% CI, 0.1–1.8).[35] In a prospective cohort study of 263 infants born in the United States, the rates for preterm births, neonatal ICU admissions, and respiratory disease did not differ between infants born to mothers with and without SARS-CoV-2 infection.[36] A cohort study from Sweden demonstrated that 5-minute Apgar scores and birth weight for gestational age did not differ between infants born to mothers with and without SARS-CoV-2 infection.[37] Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET) data from CDC that captured 598 hospitalized, pregnant women with SARS-CoV-2 infection showed a pregnancy loss rate of 2% among 458 pregnancies completed during COVID-19-related hospitalizations and a preterm birth rate of 12.9% compared to 10% for the general U.S. population.[38] A systematic review and meta-analysis of studies that included 2,567 pregnancies concluded that SARS-CoV-2-positive mothers were at increased risk of iatrogenic preterm birth. This risk was predominantly due to caesarean sections (21.8% of births) performed due to maternal illness and fear of maternal decompensation. In contrast, there was no increase in the rate of spontaneous preterm birth relative to the expected rate in pregnant individuals without SARS-CoV-2 infection.[39,40] Finally, a prospective cohort study from the United Kingdom of 66 neonates with SARS-CoV-2 infection found that 3% may have had vertically acquired infection

and 12% had suspected nosocomially acquired infection.[29] Specific guidance on the diagnosis and management of COVID-19 in neonates born to people with known or suspected SARS-CoV-2 infection is provided by CDC.

Treatment Considerations

There are no results available from clinical trials that evaluated treatments for COVID-19 in children, and observational data on the safety or efficacy of drug therapy in children with COVID-19 are extremely limited. More high-quality studies, including randomized trials, are urgently needed. Guidance for the treatment of COVID-19 in children has been published and is mostly extrapolated from recommendations for adults with COVID-19.[41,42] The older the child and the more severe the disease, the more reasonable it is to follow recommendations for adult patients with COVID-19 (see Therapeutic Management of Nonhospitalized Adults With COVID-19 and Therapeutic Management of Hospitalized Adults With COVID-19). To address the uncertain safety and efficacy of these treatment options, children should be enrolled in clinical trials and multicenter pragmatic trials whenever possible.

The majority of children with mild or moderate COVID-19 will not progress to more severe illness and thus should be managed with supportive care alone **(AIII)**. The risks and benefits of therapy should be assessed based on illness severity, age, and the presence of the risk factors outlined above.

Remdesivir

Remdesivir is the only drug approved by the Food and Drug Administration (FDA) for the treatment of COVID-19 (see Remdesivir for more information). It is approved for the treatment of COVID-19 in hospitalized adult and pediatric patients (aged ≥12 years and weighing ≥40 kg). It is also available through an FDA Emergency Use Authorization (EUA) for the treatment of COVID-19 in hospitalized pediatric patients weighing 3.5 kg to <40 kg or aged <12 years and weighing ≥3.5 kg.[43] Remdesivir has not been evaluated in clinical trials that include children, and there have been no results from systematic evaluations of pharmacokinetics, efficacy, or toxicity in younger children, although studies are ongoing (see ClinicalTrials.gov). However, based on adult data, the potential benefits of remdesivir are likely to be greater for hospitalized children with COVID-19 who are at higher risk of progression due to older age (i.e., aged ≥16 years) or medical conditions than for those without these risk factors. **Remdesivir** is recommended for hospitalized children aged ≥12 years with COVID-19 who have risk factors for severe disease and have an emergent or increasing need for supplemental oxygen **(BIII)**. **Remdesivir** is also recommended for hospitalized children aged ≥16 years with COVID-19 who have an emergent or increasing need for supplemental oxygen even in the absence of risk factors **(BIII)**. **Remdesivir** can be considered for other hospitalized children of all ages with COVID-19 who have an emergent or increasing need for supplemental oxygen in consultation with a pediatric infectious disease specialist **(CIII)**.

Dexamethasone

Dexamethasone is recommended for the treatment of hospitalized adults with COVID-19 who require mechanical ventilation or supplemental oxygen through a high-flow device (see Corticosteroids and Therapeutic Management of Hospitalized Adults With COVID-19 for more information). The safety and effectiveness of dexamethasone or other corticosteroids for COVID-19 treatment have not been sufficiently evaluated in pediatric patients; thus, caution is warranted when extrapolating recommendations for adults to patients aged <18 years. The COVID-19 Treatment Guidelines Panel (the Panel) recommends using **dexamethasone** for children with COVID-19 who require high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) **(BIII)**. It is not routinely recommended for pediatric patients who require only low levels of oxygen support (i.e., via a nasal cannula only). Use of dexamethasone for the treatment of severe

COVID-19 in children who are profoundly immunocompromised has not been evaluated, may be harmful, and therefore should be considered only on a case-by-case basis. If dexamethasone is not available, alternative glucocorticoids such as prednisone, methylprednisolone, or hydrocortisone can be considered. The dexamethasone dosing regimen for pediatric patients is dexamethasone 0.15 mg/kg/dose (maximum dose 6 mg) once daily for up to 10 days.

Anti-SARS-CoV-2 Monoclonal Antibodies

Although EUAs have been issued for bamlanivimab plus etesevimab, casirivimab plus imdevimab, and sotrovimab for the treatment of nonhospitalized, high-risk patients aged ≥12 years and weighing ≥40 kg with mild to moderate COVID-19, there are currently no data available to determine which high-risk pediatric patients defined in the EUAs will likely benefit from these therapies. Consequently, there is insufficient evidence for the Panel to recommend either for or against the use of these anti-SARS-CoV-2 mAbs in children with COVID-19 who are not hospitalized but are at high risk of severe disease and/or hospitalization. In consultation with a pediatric infectious disease specialist, anti-SARS-CoV-2 mAb can be considered on a case-by-case basis for children who meet the EUA criteria but should not be considered routine care. This recommendation is primarily based on the absence of data assessing the efficacy and safety in children and adolescents, limited data with which to identify children who are at the highest risk of severe COVID-19, the low overall risk of progression to serious disease in children, and the potential risk associated with infusion reactions.

Additional guidance is provided in a recent publication endorsed by the Pediatric Infectious Diseases Society.[25] There are currently no data to support the use of anti-SARS-CoV-2 mAbs in hospitalized children for COVID-19. Emerging data regarding the prevalence and clinical significance of SARS-CoV-2 variants, and the efficacy of mAbs against variants, may inform the choice of specific anti-SARS-CoV-2 mAb therapies in the future.

Convalescent Plasma

FDA has also issued an EUA for the use of high-titer convalescent plasma for the treatment of hospitalized patients with COVID-19 (see Convalescent Plasma for more information).[44] The safety and efficacy of convalescent plasma have not been evaluated in pediatric patients with COVID-19. There is insufficient evidence for the Panel to recommend either for or against the use of convalescent plasma for the treatment of COVID-19 in either pediatric outpatients or in hospitalized children who do not require mechanical ventilation. The Panel **recommends against** the use of **convalescent plasma** for pediatric patients with COVID-19 who are mechanically ventilated **(AIII)**. In consultation with a pediatric infectious disease specialist, convalescent plasma may be considered on a case-by-case basis for children who meet the EUA criteria for its use.

Baricitinib

FDA has also issued an EUA for the use of baricitinib in combination with remdesivir in hospitalized adults and children aged ≥2 years with COVID-19 who require supplemental oxygen, mechanical ventilation, or ECMO.[45] The safety and efficacy of baricitinib have not been evaluated in pediatric patients with COVID-19, and pediatric data regarding its use for other conditions are extremely limited. Thus, there is insufficient evidence for the Panel to recommend either for or against the use of baricitinib in combination with remdesivir for the treatment of COVID-19 in hospitalized children in whom corticosteroids cannot be used (see Kinase Inhibitors for more information).

Tocilizumab

Data on the use of tocilizumab for the treatment of non-COVID-19 conditions in children are limited to very specific clinical scenarios (e.g., chimeric antigen receptor T cell-related cytokine release

syndrome).[46] The use of tocilizumab for severe cases of acute COVID-19 has been described in pediatric case series.[14,47] Data on tocilizumab efficacy from trials in adults with COVID-19 are conflicting, and benefit has only been demonstrated in a subset of hospitalized patients (see Interleukin-6 Inhibitors). There is insufficient evidence for the Panel to recommend either for or against the use of tocilizumab for hospitalized children with COVID-19 or MIS-C. If used, tocilizumab should be used in combination with dexamethasone. The Panel **recommends against** the use of **sarilumab** for hospitalized children with COVID-19 or MIS-C, except in a clinical trial **(AIII)**.

As for other agents outlined in these Guidelines, there is insufficient evidence for the Panel to recommend either for or against the use of specific antivirals or immunomodulatory agents for the treatment of COVID-19 in pediatric patients. Considerations such as underlying conditions, disease severity, and the potential for drug toxicity or drug interactions may inform decisions on the use of these agents in pediatric patients with COVID-19 on a case-by-case basis. Children should be enrolled in clinical trials that are evaluating COVID-19 therapies whenever possible. A number of additional drugs are being investigated for the treatment of COVID-19 in adults; refer to the Antiviral Therapy and Immunomodulators sections to review special considerations for using these drugs in children and refer to Table 2f and Table 4f for recommendations on pediatric dosing regimens.

Multisystem Inflammatory Syndrome in Children

A small subset of children and young adults with SARS-CoV-2 infection develop MIS-C. This immune manifestation is also referred to as pediatric multisystem inflammatory syndrome-temporally associated with SARS-CoV-2 (PMIS-TS), although the case definitions for the syndromes differ slightly. This syndrome was first described in Europe, where previously healthy children with severe inflammation and Kawasaki disease-like features were identified to have current or recent infection with SARS-CoV-2. The clinical spectrum of MIS-C has been described in the United States and is similar to that described for PMIS-TS. MIS-C is consistent with a post-infectious inflammatory syndrome related to SARS-CoV-2.[48,49] Most MIS-C patients have serologic evidence of previous SARS-CoV-2 infection, but only a minority are RT-PCR positive for SARS-CoV-2 at presentation.[50,51] The peak incidence of MIS-C lags about 4 weeks behind the peak of acute pediatric COVID-19 hospitalizations. Emerging data suggests that adults may also develop a similar syndrome, multisystem inflammatory syndrome in adults (MIS-A), although it is not clear if this is a postinfectious complication similar to MIS-C.[50-52] Although risk factors for MIS-C have not been established, in an analysis of MIS-C cases in the United States, most of the children were non-White, and obesity was the most common comorbidity.[53] Unlike in children with acute COVID-19, the majority of children who present with MIS-C do not seem to have underlying comorbid conditions other than obesity.

Clinical Manifestations

The current CDC case definition for MIS-C includes:

- An individual aged <21 years presenting with fever,[a] laboratory evidence of inflammation,[b] and evidence of clinically severe illness that requires hospitalization with multisystem (i.e., >2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological); *and*
- No alternative plausible diagnoses; *and*
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, antigen test, or serology results; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms.[54]

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

[b] Including, but not limited to, 1 or more of the following: an elevated C-reactive protein, erythrocyte sedimentation rate,

fibrinogen, procalcitonin, D-dimer, ferritin, lactate dehydrogenase, interleukin-6, or neutrophils, or reduced lymphocytes or albumin levels

Distinguishing MIS-C from other febrile illnesses in the community setting remains challenging, but the presence of persistent fever, multisystem manifestations, and laboratory abnormalities could help early recognition.[55] The clinical spectrum of hospitalized cases has included younger children with mucocutaneous manifestations that overlap with Kawasaki disease, older children with more multiorgan involvement and shock, and patients with respiratory manifestations that overlap with acute COVID-19. Patients with MIS-C are often critically ill, and up to 80% of children require ICU admission.[53] Most patients with MIS-C have markers of cardiac injury or dysfunction, including elevated levels of troponin and brain natriuretic protein.[50,51] Echocardiographic findings in these cases include impaired left ventricular function and coronary artery dilations, and, rarely, coronary artery aneurysms. The reported mortality rate in the United States for hospitalized children with MIS-C is 1% to 2%. Longitudinal studies are currently ongoing to examine the long-term sequelae of MIS-C.

The pathogenesis of MIS-C is still being elucidated. Differences have been demonstrated between MIS-C and typical Kawasaki disease in terms of epidemiology, cytopenias, cytokine expression, and elevation of inflammatory markers. Immunologic profiling has also shown differences in cytokine expression (tumor necrosis factor alpha and interleukin-10) between MIS-C and acute COVID-19 in children.[56-58]

Management

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

References

1. Centers for Disease Control and Prevention. Information for pediatric healthcare providers. 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/pediatric-hcp.html. Accessed February 15, 2022.
2. Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 among children in China. *Pediatrics*. 2020;145(6). Available at: https://www.ncbi.nlm.nih.gov/pubmed/32179660.
3. CDC COVID Response Team. Coronavirus disease 2019 in children—United States, February 12–April 2, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(14):422-426. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32271728.
4. Cui X, Zhang T, Zheng J, et al. Children with coronavirus disease 2019: a review of demographic, clinical, laboratory, and imaging features in pediatric patients. *J Med Virol*. 2020;92(9):1501-1510. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32418216.
5. Livingston E, Bucher K. Coronavirus disease 2019 (COVID-19) in Italy. *JAMA*. 2020;323(14):1335. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32181795.
6. Tagarro A, Epalza C, Santos M, et al. Screening and severity of coronavirus disease 2019 (COVID-19) in children in Madrid, Spain. *JAMA Pediatr*. 2020;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32267485.
7. DeBiasi RL, Song X, Delaney M, et al. Severe coronavirus disease-2019 in children and young adults in the Washington, DC, metropolitan region. *J Pediatr*. 2020;223:199-203 e191. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32405091.
8. Chao JY, Derespina KR, Herold BC, et al. Clinical characteristics and outcomes of hospitalized and critically ill children and adolescents with coronavirus disease 2019 at a tertiary care medical center in New York City. *J Pediatr*. 2020;223:14-19 e12. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32407719.

9. Swann OV, Holden KA, Turtle L, et al. Clinical characteristics of children and young people admitted to hospital with COVID-19 in United Kingdom: prospective multicentre observational cohort study. *BMJ*. 2020;370:m3249. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32960186.
10. Gotzinger F, Santiago-Garcia B, Noguera-Julian A, et al. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. *Lancet Child Adolesc Health*. 2020;4(9):653-661. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32593339.
11. Kim L, Whitaker M, O'Halloran A, et al. Hospitalization rates and characteristics of children aged <18 years hospitalized with laboratory-confirmed COVID-19—COVID-NET, 14 States, March 1–July 25, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(32):1081-1088. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32790664.
12. Poline J, Gaschignard J, Leblanc C, et al. Systematic severe acute respiratory syndrome coronavirus 2 screening at hospital admission in children: a French prospective multicenter study. *Clin Infect Dis*. 2021;72(12):2215-2217. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32710743.
13. Leidman E, Duca LM, Omura JD, et al. COVID-19 trends among persons aged 0-24 years—United States, March 1-December 12, 2020. *MMWR Morb Mortal Wkly Rep*. 2021;70(3):88-94. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33476314.
14. Shekerdemian LS, Mahmood NR, Wolfe KK, et al. Characteristics and outcomes of children with coronavirus disease 2019 (COVID-19) infection admitted to US and Canadian pediatric intensive care units. *JAMA Pediatr*. 2020;174(9):868-873. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32392288.
15. Bixler D, Miller AD, Mattison CP, et al. SARS-CoV-2-associated deaths among persons aged <21 years—United States, February 12–July 31, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(37):1324-1329. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32941417.
16. Goss MB, Galvan NTN, Ruan W, et al. The pediatric solid organ transplant experience with COVID-19: an initial multi-center, multi-organ case series. *Pediatr Transplant*. 2021;25(3):e13868. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32949098.
17. Bisogno G, Provenzi M, Zama D, et al. Clinical characteristics and outcome of severe acute respiratory syndrome coronavirus 2 infection in Italian pediatric oncology patients: a study from the infectious diseases working group of the Associazione Italiana di Oncologia e Ematologia Pediatrica. *J Pediatric Infect Dis Soc*. 2020;9(5):530-534. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32652521.
18. Boulad F, Kamboj M, Bouvier N, Mauguen A, Kung AL. COVID-19 in children with cancer in New York City. *JAMA Oncol*. 2020;6(9):1459-1460. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32401276.
19. de Rojas T, Perez-Martinez A, Cela E, et al. COVID-19 infection in children and adolescents with cancer in Madrid. *Pediatr Blood Cancer*. 2020;67(7):e28397. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32383819.
20. Hrusak O, Kalina T, Wolf J, et al. Flash survey on severe acute respiratory syndrome coronavirus-2 infections in paediatric patients on anticancer treatment. *Eur J Cancer*. 2020;132:11-16. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32305831.
21. Freeman MC, Rapsinski GJ, Zilla ML, Wheeler SE. Immunocompromised seroprevalence and course of illness of SARS-CoV-2 in one pediatric quaternary care center. *J Pediatric Infect Dis Soc*. 2021;10(4):426-431. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33049042.
22. Madhusoodhan PP, Pierro J, Musante J, et al. Characterization of COVID-19 disease in pediatric oncology patients: the New York-New Jersey regional experience. *Pediatr Blood Cancer*. 2021;68(3):e28843. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33338306.
23. Lewis MJ, Anderson BR, Fremed M, et al. Impact of coronavirus disease 2019 (COVID-19) on patients with congenital heart disease across the lifespan: the experience of an academic congenital heart disease center in New York City. *J Am Heart Assoc*. 2020;9(23):e017580. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33196343.

24. Chiotos K, Hayes M, Kimberlin DW, et al. Multicenter interim guidance on use of antivirals for children with coronavirus disease 2019/severe acute respiratory syndrome coronavirus 2. *J Pediatric Infect Dis Soc*. 2021;10(1):34-48. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32918548.

25. Wolf J, Abzug MJ, Wattier RL, et al. Initial guidance on use of monoclonal antibody therapy for treatment of coronavirus disease 2019 in children and adolescents. *J Pediatric Infect Dis Soc*. 2021;10(5):629-634. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33388760.

26. Rajpal S, Tong MS, Borchers J, et al. Cardiovascular magnetic resonance findings in competitive athletes recovering from COVID-19 infection. *JAMA Cardiol*. 2021;6(1):116-118. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32915194.

27. Demirjian A, Singh C, Tebruegge M, et al. Probable vertical transmission of SARS-CoV-2 infection. *Pediatr Infect Dis J*. 2020;39(9):e257-e260. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32658096.

28. Dong L, Tian J, He S, et al. Possible vertical transmission of SARS-CoV-2 from an infected mother to her newborn. *JAMA*. 2020;323(18):1846-1848. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32215581.

29. Gale C, Quigley MA, Placzek A, et al. Characteristics and outcomes of neonatal SARS-CoV-2 infection in the UK: a prospective national cohort study using active surveillance. *Lancet Child Adolesc Health*. 2021;5(2):113-121. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33181124.

30. Chen H, Guo J, Wang C, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet*. 2020;395(10226):809-815. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32151335.

31. Fan C, Lei D, Fang C, et al. Perinatal transmission of 2019 coronavirus disease-associated severe acute respiratory syndrome coronavirus 2: should we worry? *Clin Infect Dis*. 2021;72(5):862-864. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32182347.

32. Zeng L, Xia S, Yuan W, et al. Neonatal early-onset infection with SARS-CoV-2 in 33 neonates born to mothers with COVID-19 in Wuhan, China. *JAMA Pediatr*. 2020;174(7):722-725. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32215598.

33. Von Kohorn I, Stein SR, Shikani BT, et al. In utero severe acute respiratory syndrome coronavirus 2 infection. *J Pediatric Infect Dis Soc*. 2020;9(6):769-771. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33089311.

34. Dumitriu D, Emeruwa UN, Hanft E, et al. Outcomes of neonates born to mothers with severe acute respiratory syndrome coronavirus 2 infection at a large medical center in New York City. *JAMA Pediatr*. 2021;175(2):157-167. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33044493.

35. Huntley BJF, Huntley ES, Di Mascio D, et al. Rates of maternal and perinatal mortality and vertical transmission in pregnancies complicated by severe acute respiratory syndrome coronavirus 2 (SARS-Co-V-2) infection: a systematic review. *Obstet Gynecol*. 2020;136(2):303-312. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32516273.

36. Flaherman VJ, Afshar Y, Boscardin WJ, et al. Infant outcomes following maternal infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): first report from the pregnancy coronavirus outcomes registry (PRIORITY) study. *Clin Infect Dis*. 2021;73(9):e2810-e2813. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32947612.

37. Ahlberg M, Neovius M, Saltvedt S, et al. Association of SARS-CoV-2 test status and pregnancy outcomes. *JAMA*. 2020;324(17):1782-1785. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32965467.

38. Delahoy MJ, Whitaker M, O'Halloran A, et al. Characteristics and maternal and birth outcomes of hospitalized pregnant women with laboratory-confirmed COVID-19—COVID-NET, 13 States, March 1–August 22, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(38):1347-1354. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32970655.

39. Khalil A, Kalafat E, Benlioglu C, et al. SARS-CoV-2 infection in pregnancy: a systematic review and meta-analysis of clinical features and pregnancy outcomes. *EClinicalMedicine*. 2020;25:100446. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32838230.

40. Khoury R, Bernstein PS, Debolt C, et al. Characteristics and outcomes of 241 births to women with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection at five New York City medical centers. *Obstet Gynecol*. 2020;136(2):273-282. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32555034.

41. Chiotos K, Hayes M, Kimberlin DW, et al. Multicenter initial guidance on use of antivirals for children with coronavirus disease 2019/severe acute respiratory syndrome coronavirus 2. *J Pediatric Infect Dis Soc*. 2020;9(6):701-715. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32318706.

42. Dulek DE, Fuhlbrigge RC, Tribble AC, et al. Multidisciplinary guidance regarding the use of immunomodulatory therapies for acute coronavirus disease 2019 in pediatric patients. *J Pediatric Infect Dis Soc*. 2020;9(6):716-737. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32808988.

43. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of veklury (remdesivir) for hospitalized pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg. 2020. Available at: https://www.fda.gov/media/137566/download.

44. Food and Drug Administration. EUA 26382: Emergency Use Authorization (EUA) decision memo. 2020. Available at: https://www.fda.gov/media/141480/download.

45. Food and Drug Administration. Letter of authorization: EUA for baricitinib (Olumiant), in combination with remdesivir (Veklury), for the treatment of suspected or laboratory confirmed coronavirus disease 2019 (COVID-19). 2020. Available at: https://www.fda.gov/media/143822/download.

46. Kotch C, Barrett D, Teachey DT. Tocilizumab for the treatment of chimeric antigen receptor T cell-induced cytokine release syndrome. *Expert Rev Clin Immunol*. 2019;15(8):813-822. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31219357.

47. Derespina KR, Kaushik S, Plichta A, et al. Clinical manifestations and outcomes of critically ill children and adolescents with coronavirus disease 2019 in New York City. *J Pediatr*. 2020;226:55-63 e52. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32681989.

48. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet*. 2020;395(10237):1607-1608. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32386565.

49. Whittaker E, Bamford A, Kenny J, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. *JAMA*. 2020;324(3):259-269. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32511692.

50. Dufort EM, Koumans EH, Chow EJ, et al. Multisystem inflammatory syndrome in children in New York State. *N Engl J Med*. 2020;383(4):347-358. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32598830.

51. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. *N Engl J Med*. 2020;383(4):334-346. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32598831.

52. Morris SB, Schwartz NG, Patel P, et al. Case series of multisystem inflammatory syndrome in adults associated with SARS-CoV-2 infection—United Kingdom and United States, March–August 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(40):1450-1456. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33031361.

53. Godfred-Cato S, Bryant B, Leung J, et al. COVID-19-associated multisystem inflammatory syndrome in children—United States, March–July 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(32):1074-1080. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32790663.

54. Centers for Disease Control and Prevention. Information for healthcare providers about multisystem inflammatory syndrome in children (MIS-C). 2021. Available at: https://www.cdc.gov/mis/mis-c/hcp/. Accessed February 15, 2022.

55. Carlin RF, Fischer AM, Pitkowsky Z, et al. Discriminating multisystem inflammatory syndrome in children requiring treatment from common febrile conditions in outpatient settings. *J Pediatr*. 2021;229:26-32 e22.

Available at: https://www.ncbi.nlm.nih.gov/pubmed/33065115.

56. Lee PY, Day-Lewis M, Henderson LA, et al. Distinct clinical and immunological features of SARS-CoV-2-induced multisystem inflammatory syndrome in children. *J Clin Invest*. 2020;130(11):5942-5950. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32701511.
57. Rowley AH, Shulman ST, Arditi M. Immune pathogenesis of COVID-19-related multisystem inflammatory syndrome in children. *J Clin Invest*. 2020;130(11):5619-5621. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32870815.
58. Diorio C, Henrickson SE, Vella LA, et al. Multisystem inflammatory syndrome in children and COVID-19 are distinct presentations of SARS-CoV-2. *J Clin Invest*. 2020;130(11):5967-5975. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32730233.

Special Considerations in Adults and Children With Cancer

Last Updated: October 19, 2021

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

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

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

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

- American Society of Clinical Oncology
- Society of Surgical Oncology
- American Society for Radiation Oncology
- International Lymphoma Radiation Oncology Group

This section of the COVID-19 Treatment Guidelines complements these sources and focuses on testing for SARS-CoV-2, managing COVID-19 in patients with cancer, and managing cancer-directed therapies during the COVID-19 pandemic. The optimal management and therapeutic approach to COVID-19 in this population has not yet been defined.

Vaccination for COVID-19 in Patients With Cancer

The clinical trials that evaluated the COVID-19 vaccines that have received Emergency Use Authorizations and/or approval from the Food and Drug Administration (FDA) excluded severely immunocompromised patients. The Advisory Committee on Immunization Practices notes that the authorized COVID-19 vaccines are not live vaccines; therefore, they can be safely administered to immunocompromised people.[7] Given the effectiveness of the COVID-19 vaccines in the general population and the increased risk of severe COVID-19 and mortality in patients with cancer, the COVID-19 Treatment Guidelines Panel (the Panel) recommends COVID-19 vaccination for patients with active cancer or patients who are receiving treatment for cancer **(AIII)**. The Centers for Disease Control and Prevention (CDC) recommends a third dose of an mRNA vaccine for patients who are receiving active cancer therapy; this third dose should be administered at least 28 days after the completion of the initial two-dose mRNA COVID-19 vaccine series.[8] ASH and NCCN have provided additional recommendations for administering a third vaccine dose in patients with cancer based on the patient's tumor type and therapy.[9,10]

The mRNA vaccines contain polyethylene glycol (PEG), and the Johnson & Johnson (J&J)/Janssen vaccine contains polysorbate. In patients who experience a severe anaphylactic reaction to PEG-asparaginase, consider performing allergy testing for PEG prior to vaccination with either of the mRNA vaccines, or consider using the J&J/Janssen vaccine with precautions.[11-13]

When determining the timing of COVID-19 vaccination in patients with cancer, clinicians should consider the following factors:

- If possible, patients who are planning to receive chemotherapy should complete vaccination for COVID-19 at least 2 weeks before starting chemotherapy.[9,14]
- In patients with hematologic malignancy who are undergoing intensive chemotherapy (e.g., induction chemotherapy for acute myelogenous leukemia), vaccination should be delayed until neutrophil recovery.[15]
- Hematopoietic stem cell and chimeric antigen receptor T cell recipients can be offered COVID-19 vaccination starting at least 3 months after therapy.[14]

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

Decreased immunologic responses to COVID-19 vaccination have been reported in patients who were receiving treatment for solid tumors and hematologic malignancies.[18,19] The type of therapy has been shown to influence the patient's response to vaccination. For example, people with chronic lymphocytic leukemia who were treated with Bruton's tyrosine kinase inhibitors or venetoclax with

or without anti-CD20 antibodies had extremely low response rates (16.0% and 13.6%, respectively).[19] In comparison, approximately 80% to 95% of patients with solid tumors showed immunologic responses.[18,20,21] Currently, it is not known how a third dose of an mRNA vaccine affects response rates in patients with cancer.

Patients with cancer are at high risk of progressing to serious COVID-19, and they may be eligible to receive anti-SARS-CoV-2 monoclonal antibodies (mAbs) as post-exposure prophylaxis (PEP).

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

Testing for SARS-CoV-2 in Patients With Cancer

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

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

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

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

Decisions about treatment regimens, surgery, and radiation therapy for the underlying malignancy should be made on a case-by-case basis, and clinicians should consider the biology of the cancer, the need for hospitalization, the number of clinic visits required, and the anticipated degree of immunosuppression. Additional factors that should be considered include the following:

- If possible, treatment delays should be avoided for curable cancers that have been shown to have worse outcomes when treatment is delayed (e.g., pediatric acute lymphoblastic leukemia).
- When deciding between equally effective treatment regimens, regimens that can be administered orally or those that require fewer infusions are preferred.[31]
- The potential risks of drug-related lung toxicity (e.g., from using bleomycin or PD-1 inhibitors)

must be balanced with the clinical efficacy of alternative regimens or the risk of delaying care.[32]

- Preventing neutropenia can decrease the risk of neutropenic fever and the need for emergency department evaluation and hospitalization. Granulocyte colony-stimulating factor (G-CSF) should be given with chemotherapy regimens that have intermediate (10% to 20%) or high (>20%) risks of febrile neutropenia.[33]
- Cancer treatment regimens that do not affect the outcomes of COVID-19 in patients with cancer may not need to be altered. In a prospective observational study, receipt of immunotherapy, hormonal therapy, or radiotherapy in the month prior to SARS-CoV-2 infection was not associated with an increased risk of mortality among patients with cancer and COVID-19.[34] A retrospective study from Italy evaluated the incidence of SARS-CoV-2 infection in patients with prostate cancer and found that 114 of 37,161 patients (0.3%) who were treated with therapies other than androgen deprivation therapy became infected, compared to 4 of 5,273 patients (0.08%) who were treated with androgen deprivation therapy (OR 4.05; 95% CI, 1.55–10.59).[35] A small cohort study of patients from Finland with prostate cancer did not find an association between androgen deprivation and the incidence of SARS-CoV-2 infection.[36] The viral spike proteins that SARS-CoV-2 uses to enter cells are primed by transmembrane serine protease 2 (TMPRSS2), an androgen-regulated gene. Whether androgen deprivation therapy protects against SARS-CoV-2 infection requires further investigation in larger cohorts or clinical trials.[35]
- Radiation therapy guidelines suggest increasing the dose per fraction and reducing the number of daily treatments to minimize the number of hospital visits.[37,38]

Blood supply shortages will likely continue during the COVID-19 pandemic due to social distancing, cancellation of blood drives, and infection among donors. The FDA has proposed revising the donor criteria to increase the number of eligible donors.[39] In patients with cancer, stricter transfusion thresholds for blood products (e.g., red blood cells, platelets) in asymptomatic patients should be considered.[8] At this time, there is no evidence that COVID-19 can be transmitted through blood products.[40,41]

Febrile Neutropenia

Patients with cancer and febrile neutropenia should undergo molecular diagnostic testing for SARS-CoV-2 and evaluation for other infectious agents; they should also be given empiric antibiotics, as outlined in the NCCN Guidelines.[42] Low-risk febrile neutropenia patients should be treated at home with oral antibiotics or intravenous infusions of antibiotics to limit nosocomial exposure to SARS-CoV-2. Patients with high-risk febrile neutropenia should be hospitalized per standard of care.[42] Empiric antibiotics should be continued per standard of care in patients who test positive for SARS-CoV-2. Clinicians should also continuously evaluate neutropenic patients for emergent infections.

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

Retrospective studies suggest that patients with cancer who were admitted to the hospital with SARS-CoV-2 infection have a high case-fatality rate, with higher rates observed in patients with hematologic malignancies than in those with solid tumors.[43,44]

The recommendations for treating COVID-19 in patients with cancer are the same as those for the general population **(AIII)**. See Therapeutic Management of Nonhospitalized Adults With COVID-19 and Therapeutic Management of Hospitalized Adults With COVID-19 for more information. Patients with cancer are at high risk of progressing to serious COVID-19, and they may be eligible to receive anti-SARS-CoV-2 mAbs as treatment if they develop mild to moderate COVID-19.

Dexamethasone treatment has been associated with a lower mortality rate in patients with COVID-19 who require supplemental oxygen or invasive mechanical ventilation.[45] In patients with cancer, dexamethasone is commonly used to prevent chemotherapy-induced nausea, as a part of tumor-directed therapy, and to treat inflammation associated with brain metastasis. The side effects of dexamethasone are expected to be the same in patients with cancer as in those without cancer. If possible, treatments that are not currently recommended for SARS-CoV-2 infection should be administered as part of a clinical trial, since the safety and efficacy of these agents have not been well-defined in patients with cancer.

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

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

Medication Interactions

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

Several antineoplastic medications may interact with therapies that are being investigated for COVID-19.[50,51] For example, tocilizumab can interact with vincristine and doxorubicin. Any COVID-19 therapy that may cause QT prolongation must be used with caution in patients who are being treated with venetoclax, gilteritinib, or tyrosine kinase inhibitor therapy (e.g., nilotinib). Dexamethasone is commonly used as an antiemetic for patients with cancer and is recommended for the treatment of certain patients with COVID-19 (see Therapeutic Management of Hospitalized Adults With COVID-19). Dexamethasone is a weak to moderate cytochrome P450 (CYP) 3A4 inducer; therefore, interactions with any CYP3A4 substrates need to be considered.

Special Considerations in Children

Preliminary published reports suggest that pediatric patients with cancer may have milder manifestations of COVID-19 than adult patients with cancer, although larger studies are needed.[52-54] Guidance on managing children with cancer during the COVID-19 pandemic is available from an international group that received input from the International Society of Paediatric Oncology, the Children's Oncology Group, St. Jude Global, and Childhood Cancer International.[55] Two publications include guidance for managing specific malignancies, guidance for supportive care, and a summary of web links from expert groups that are relevant to the care of pediatric oncology patients during the COVID-19 pandemic.[55,56]

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

References

1. Dai M, Liu D, Liu M, et al. Patients with cancer appear more vulnerable to SARS-CoV-2: a multicenter study during the COVID-19 outbreak. *Cancer Discov*. 2020;10(6):783-791. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32345594.
2. Shah V, Ko Ko T, Zuckerman M, et al. Poor outcome and prolonged persistence of SARS-CoV-2 RNA in COVID-19 patients with haematological malignancies; King's College Hospital experience. *Br J Haematol*. 2020;190(5):e279-e282. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32526039.
3. Yang K, Sheng Y, Huang C, et al. Clinical characteristics, outcomes, and risk factors for mortality in patients with cancer and COVID-19 in Hubei, China: a multicentre, retrospective, cohort study. *Lancet Oncol*. 2020;21(7):904-913. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32479787.
4. Robilotti EV, Babady NE, Mead PA, et al. Determinants of COVID-19 disease severity in patients with cancer. *Nat Med*. 2020;26(8):1218-1223. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32581323.
5. Giannakoulis VG, Papoutsi E, Siempos, II. Effect of cancer on clinical outcomes of patients with COVID-19: a meta-analysis of patient data. *JCO Glob Oncol*. 2020;6:799-808. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32511066.
6. Kuderer NM, Choueiri TK, Shah DP, et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. *Lancet*. 2020;395(10241):1907-1918. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32473681.
7. Centers for Disease Control and Prevention. Current COVID-19 ACIP vaccine recommendations. 2021. Available at: https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/covid-19.html. Accessed September 30, 2021.
8. Centers for Disease Control and Prevention. COVID-19 vaccines for moderately to severely immunocompromised people. 2021. Available at: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html. Accessed September 9, 2021.
9. American Society of Hematology. General principles of COVID-19 vaccines for immunocompromised patients. 2021. Available at: https://www.hematology.org/covid-19/ash-astct-covid-19-and-vaccines. Accessed September 16, 2021.
10. National Comprehensive Cancer Network. Recommendations of the National Comprehensive Cancer Network (NCCN) COVID-19 Vaccination Advisory Committee. 2021. Available at: https://www.nccn.org/docs/default-source/covid-19/2021_covid-19_vaccination_guidance_v4-0.pdf?sfvrsn=b483da2b_68. Accessed September 16, 2021.
11. American Society of Hematology. COVID-19 and pediatric ALL: frequently asked questions. 2021. Available at: https://www.hematology.org/covid-19/covid-19-and-pediatric-all. Accessed September 30, 2021.
12. Centers for Disease Control and Prevention. COVID-19 vaccines for people with allergies. 2021. Available at: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/specific-groups/allergies.html. Accessed September 16, 2021.
13. Centers for Disease Control and Prevention. Interim clinical considerations for use of COVID-19 vaccines currently approved or authorized in the United States. 2021. Available at: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html. Accessed September 16, 2021.
14. American Society of Hematology. ASH-ASTCT COVID-19 vaccination for HCT and CAR T cell recipients: frequently asked questions 2021. Available at: https://www.hematology.org/covid-19/ash-astct-covid-19-vaccination-for-hct-and-car-t-cell-recipients. Accessed September 16, 2021.
15. National Comprehensive Cancer Network. COVID-19 resources. 2021. Available at: https://www.nccn.org/covid-19. Accessed September 16, 2021.

16. Chen YW, Tucker MD, Beckermann KE, Iams WT, Rini BI, Johnson DB. COVID-19 mRNA vaccines and immune-related adverse events in cancer patients treated with immune checkpoint inhibitors. *Eur J Cancer*. 2021;155:291-293. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34400057.

17. Waissengrin B, Agbarya A, Safadi E, Padova H, Wolf I. Short-term safety of the BNT162b2 mRNA COVID-19 vaccine in patients with cancer treated with immune checkpoint inhibitors. *Lancet Oncol*. 2021;22(5):581-583. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33812495.

18. Barriere J, Chamorey E, Adjtoutah Z, et al. Impaired immunogenicity of BNT162b2 anti-SARS-CoV-2 vaccine in patients treated for solid tumors. *Ann Oncol*. 2021;32(8):1053-1055. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33932508.

19. Herishanu Y, Avivi I, Aharon A, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. *Blood*. 2021;137(23):3165-3173. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33861303.

20. Massarweh A, Eliakim-Raz N, Stemmer A, et al. Evaluation of seropositivity following BNT162b2 messenger RNA vaccination for SARS-CoV-2 in patients undergoing treatment for cancer. *JAMA Oncol*. 2021;7(8):1133-1140. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34047765.

21. Shroff RT, Chalasani P, Wei R, et al. Immune response to COVID-19 mRNA vaccines in patients with solid tumors on active, immunosuppressive cancer therapy. *medRxiv*. 2021;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.05.13.21257129v1.

22. Becker PS, Griffiths EA, Alwan LM, et al. NCCN guidelines insights: mematopoietic growth factors, version 1.2020. *J Natl Compr Canc Netw*. 2020;18(1):12-22. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31910384.

23. Yarza R, Bover M, Paredes D, et al. SARS-CoV-2 infection in cancer patients undergoing active treatment: analysis of clinical features and predictive factors for severe respiratory failure and death. *Eur J Cancer*. 2020;135:242-250. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32586724.

24. American Society of Clinical Oncology. ASCO special report: a guide to cancer care delivery during the COVID-19 pandemic. 2021. Available at: https://www.asco.org/sites/new-www.asco.org/files/content-files/2020-ASCO-Guide-Cancer-COVID19.pdf. Accessed September 16, 2021.

25. American Society of Anesthesiologists. The ASA and APSF joint statement on perioperative testing for the COVID-19 virus. 2020. Available at: https://www.asahq.org/about-asa/newsroom/news-releases/2020/06/asa-and-apsf-joint-statement-on-perioperative-testing-for-the-covid-19-virus. Accessed September 30, 2021.

26. Centers for Disease Control and Prevention. Coronavirus Disease 2019 (COVID-19): framework for healthcare systems providing non-COVID-19 clinical care during the COVID-19 pandemic. 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/framework-non-COVID-care.html. Accessed August 3, 2020.

27. Wang X, Zhou Q, He Y, et al. Nosocomial outbreak of COVID-19 pneumonia in Wuhan, China. *Eur Respir J*. 2020;55(6). Available at: https://www.ncbi.nlm.nih.gov/pubmed/32366488.

28. Luong-Nguyen M, Hermand H, Abdalla S, et al. Nosocomial infection with SARS-CoV-2 within Departments of Digestive Surgery. *J Visc Surg*. 2020;157(3S1):S13-S18. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32381426.

29. Rivett L, Sridhar S, Sparkes D, et al. Screening of healthcare workers for SARS-CoV-2 highlights the role of asymptomatic carriage in COVID-19 transmission. *Elife*. 2020;9. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32392129.

30. Centers for Disease Control and Prevention. COVID-19: how to protect yourself & others. 2021. Available at: https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html. Accessed September 30, 2021.

31. American Society of Clinical Oncology. Cancer treatment & supportive care. 2020. Available at: https://www.asco.org/covid-resources/patient-care-info/cancer-treatment-supportive-care. Accessed September 16, 2021.

32. American Society of Hematology. COVID-19 and Hodgkin lymphoma: frequently asked questions. 2021. Available at: https://www.hematology.org/covid-19/covid-19-and-hodgkin-lymphoma. Accessed September 16, 2021.

33. Griffiths EA, Alwan LM, Bachiashvili K, et al. Considerations for use of hematopoietic growth factors in patients with cancer related to the COVID-19 pandemic. *J Natl Compr Canc Netw*. 2020:1-4. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32871558.

34. Lee LYW, Cazier JB, Starkey T, et al. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. *Lancet*. 2020;395(10241):1919-1926. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32473682.

35. Montopoli M, Zumerle S, Vettor R, et al. Androgen-deprivation therapies for prostate cancer and risk of infection by SARS-CoV-2: a population-based study (N = 4532). *Ann Oncol*. 2020;31(8):1040-1045. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32387456.

36. Koskinen M, Carpen O, Honkanen V, et al. Androgen deprivation and SARS-CoV-2 in men with prostate cancer. *Ann Oncol*. 2020;31(10):1417-1418. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32615154.

37. American Society for Radiation Oncology. COVID-19 recommendations and information: COVID-19 clinical guidance. 2020. Available at: https://www.astro.org/Daily-Practice/COVID-19-Recommendations-and-Information/Clinical-Guidance. Accessed August 3, 2020.

38. Yahalom J, Dabaja BS, Ricardi U, et al. ILROG emergency guidelines for radiation therapy of hematological malignancies during the COVID-19 pandemic. *Blood*. 2020;135(21):1829-1832. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32275740.

39. Food and Drug Administration. Coronavirus (COVID-19) update: FDA provides updated guidance to address the urgent need for blood during the pandemic. 2020. Available at: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-provides-updated-guidance-address-urgent-need-blood-during-pandemic. Accessed August 3, 2020.

40. Food and Drug Administration. COVID-19 frequently asked questions. 2020. Available at: https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-frequently-asked-questions. Accessed August 3, 2020.

41. Centers for Disease Control and Prevention. Clinical questions about COVID-19: questions and answers. 2021. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/faq.html#Transmission. Accessed September 30, 2021.

42. National Comprehensive Cancer Network. NCCN best practices guidance: management of COVID-19 infection in patients with cancer. 2021. Available at: https://www.nccn.org/docs/default-source/covid-19/2021-covid-infectious-disease-management.pdf?sfvrsn=63f70c30_7.

43. Mehta V, Goel S, Kabarriti R, et al. Case fatality rate of cancer patients with COVID-19 in a New York Hospital System. *Cancer Discov*. 2020;10(7):935-941. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32357994.

44. Meng Y, Lu W, Guo E, et al. Cancer history is an independent risk factor for mortality in hospitalized COVID-19 patients: a propensity score-matched analysis. *J Hematol Oncol*. 2020;13(1):75. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32522278.

45. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with COVID-19. *N Engl J Med*. 2021;384(8):693-704. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32678530.

46. Nawar T, Morjaria S, Kaltsas A, et al. Granulocyte-colony stimulating factor in COVID-19: Is it stimulating more than just the bone marrow? *Am J Hematol*. 2020;95(8):E210-E213. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32419212.

47. National Comprehensive Cancer Network. NCCN hematopoietic growth factors: short-term recommendations specific to issues with COVID-19 (SARS-CoV-2). 2020. Available at:

https://www.nccn.org/covid-19/pdf/HGF_COVID-19.pdf.

48. van Arkel ALE, Rijpstra TA, Belderbos HNA, van Wijngaarden P, Verweij PE, Bentvelsen RG. COVID-19-associated pulmonary aspergillosis. *Am J Respir Crit Care Med*. 2020;202(1):132-135. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32396381.
49. Alanio A, Delliere S, Fodil S, Bretagne S, Megarbane B. Prevalence of putative invasive pulmonary aspergillosis in critically ill patients with COVID-19. *Lancet Respir Med*. 2020;8(6):e48-e49. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32445626.
50. American Society of Hematology. COVID-19 resources. 2020. Available at: https://www.hematology.org/covid-19. Accessed August 3, 2020.
51. University of Liverpool. COVID-19 drug interactions. 2021. Available at: https://www.covid19-druginteractions.org/.
52. Hrusak O, Kalina T, Wolf J, et al. Flash survey on severe acute respiratory syndrome coronavirus-2 infections in paediatric patients on anticancer treatment. *Eur J Cancer*. 2020;132:11-16. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32305831.
53. Andre N, Rouger-Gaudichon J, Brethon B, et al. COVID-19 in pediatric oncology from French pediatric oncology and hematology centers: High risk of severe forms? *Pediatr Blood Cancer*. 2020;67(7):e28392. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32383827.
54. de Rojas T, Perez-Martinez A, Cela E, et al. COVID-19 infection in children and adolescents with cancer in Madrid. *Pediatr Blood Cancer*. 2020;67(7):e28397. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32383819.
55. Sullivan M, Bouffet E, Rodriguez-Galindo C, et al. The COVID-19 pandemic: a rapid global response for children with cancer from SIOP, COG, SIOP-E, SIOP-PODC, IPSO, PROS, CCI, and St. Jude Global. *Pediatr Blood Cancer.* 2020;67(7):e28409. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32400924.
56. Bouffet E, Challinor J, Sullivan M, Biondi A, Rodriguez-Galindo C, Pritchard-Jones K. Early advice on managing children with cancer during the COVID-19 pandemic and a call for sharing experiences. *Pediatr Blood Cancer*. 2020;67(7):e28327. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32239747.
57. Chiotos K, Hayes M, Kimberlin DW, et al. Multicenter initial guidance on use of antivirals for children with COVID-19/SARS-CoV-2. *J Pediatric Infect Dis Soc*. 2020;9(6):701-715. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32318706.

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

Last Updated: October 19, 2021

Summary Recommendations

Vaccination for COVID-19

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

Potential Transplant and Cellular Immunotherapy Candidates

- The Panel recommends diagnostic molecular testing for SARS-CoV-2 for all potential solid organ transplant, HCT, and cellular immunotherapy candidates with signs and symptoms that suggest acute COVID-19 **(AIII)**.
- The Panel recommends following the guidance from medical professional organizations that specialize in providing care for solid organ transplant, HCT, or cellular immunotherapy recipients when performing diagnostic molecular testing for SARS-CoV-2 in these patients **(AIII)**.
- If SARS-CoV-2 is detected or if infection is strongly suspected, transplantation should be deferred, if possible **(BIII)**.
- The optimal management and therapeutic approach to COVID-19 in these populations is unknown. At this time, the procedures for evaluating and managing COVID-19 in transplant candidates are the same as those for nontransplant candidates **(AIII)**.
- Additionally, many transplant candidates are at high risk of progressing to serious COVID-19, and they may be eligible to receive anti-SARS-CoV-2 monoclonal antibodies (mAbs) for treatment or post-exposure prophylaxis (PEP).

Potential Transplant Donors

- The Panel recommends assessing all potential solid organ transplant and HCT donors for signs and symptoms that are associated with COVID-19 according to guidance from medical professional organizations **(AIII)**.
  - The Panel recommends performing diagnostic molecular testing for SARS-CoV-2 if symptoms are present **(AIII)**.
  - If SARS-CoV-2 is detected or if infection is strongly suspected, donation should be deferred **(BIII)**.

Transplant and Cellular Immunotherapy Recipients With COVID-19

- Clinicians should follow the guidelines for evaluating and managing COVID-19 in nontransplant patients when treating transplant and cellular immunotherapy recipients **(AIII)**. See Therapeutic Management of Hospitalized Adults With COVID-19 for more information.
- Immunocompromised patients with mild to moderate COVID-19 are at high risk of progressing to serious disease, and they may be eligible to receive anti-SARS-CoV-2 mAbs for treatment or PEP.
- The Panel recommends that clinicians who are treating COVID-19 in transplant and cellular immunotherapy patients consult with a transplant specialist before adjusting immunosuppressive medications **(AIII)**.
- When treating COVID-19, clinicians should pay careful attention to potential drug-drug interactions and overlapping toxicities with immunosuppressants, prophylactic antimicrobials, and other medications **(AIII)**.

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

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

Introduction

Treating COVID-19 in solid organ transplant, hematopoietic stem cell transplant (HCT), and cellular immunotherapy recipients can be challenging due to the presence of coexisting medical conditions, transplant-related cytopenias, and the need for chronic immunosuppressive therapy to prevent graft rejection and graft-versus-host disease. Transplant recipients may also have increased exposure to SARS-CoV-2 given their frequent contact with the health care system. Since immunosuppressive agents modulate several aspects of the host's immune response, the severity of COVID-19 could potentially be affected by the type and the intensity of the immunosuppressive effect of the agent, as well as by specific combinations of immunosuppressive agents. Some transplant recipients have medical comorbidities that have been associated with more severe cases of COVID-19 and a greater risk of mortality, which makes the impact of transplantation on disease severity difficult to assess.

The International Society for Heart and Lung Transplantation, the American Society of Transplantation, the American Society for Transplantation and Cellular Therapy (ASTCT), and the European Society for Blood and Marrow Transplantation (EBMT) provide guidance for clinicians who are caring for transplant recipients with COVID-19 and guidance on screening potential donors and transplant or cellular immunotherapy candidates. In addition, the American Society of Hematology offers guidance regarding COVID-19 vaccination for transplant and cellular immunotherapy recipients. This section of the COVID-19 Treatment Guidelines complements these sources and focuses on considerations for managing COVID-19 in 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 for more information. The medications that are used to treat COVID-19 may present different risks and benefits to transplant patients and nontransplant patients.

Vaccination for COVID-19 in Solid Organ Transplant, Hematopoietic Stem Cell Transplant, and Cellular Immunotherapy Candidates, Donors, and Recipients

The clinical trials that evaluated the safety and efficacy of the COVID-19 vaccines excluded severely immunocompromised patients.[1-3] The Advisory Committee on Immunization Practices notes that the currently authorized or approved COVID-19 vaccines are not live vaccines; therefore, they can be safely administered to immunocompromised people.[4] Compared to healthy vaccine recipients, solid organ transplant recipients have a reduced antibody response following a primary two-dose vaccine series of mRNA vaccines.[5-7] Among those who had no detectable antibody response to the initial two-dose vaccine series, 33% to 50% of patients developed an antibody response to an additional mRNA vaccine dose.[8,9]

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

- Received a solid organ transplant and are taking immunosuppressive medications
- Received an HCT within the last 2 years or who are taking immunosuppressive medications

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

- Ideally, solid organ transplant candidates should receive COVID-19 vaccines while they are awaiting transplant.
- In general, vaccination should be completed at least 2 weeks prior to a solid organ transplant or started 1 month after a solid organ transplant.
- In certain situations, it may be appropriate to delay vaccination until 3 months after a solid organ transplant, such as when T cell- or B cell-ablative therapy (with antithymocyte globulin or rituximab) is used at the time of transplant.[11]
- At this time, reducing the dose of immunosuppressants and holding immunosuppressants prior to vaccination **are not recommended**.
- COVID-19 vaccines can be offered as early as 3 months after a patient receives HCT or chimeric antigen receptor T cell therapy, although the efficacy of the vaccines may be reduced compared to the efficacy observed in the general population.[12-14] Patients who are scheduled to receive cytotoxic or B cell-depleting therapies should complete their COVID-19 vaccination prior to initiation or between cycles of cytotoxic or B cell-depleting therapies, if possible.
- After completing COVID-19 vaccination, immunocompromised persons should be advised to continue to exercise precautions to reduce their risk of SARS-CoV-2 exposure and infection (e.g., they should continue wearing a mask, maintain a distance of 6 feet from others, and avoid crowds and poorly ventilated spaces).[15]

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

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

Post-Exposure Prophylaxis for Transplant and Cellular Immunotherapy Recipients

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

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

The risk of transmission of SARS-CoV-2 from donors to candidates is unknown. The probability that a donor or candidate may have SARS-CoV-2 infection can be estimated by considering the epidemiologic risk, obtaining a clinical history, and testing with molecular techniques. No current testing strategy is sensitive enough or specific enough to totally exclude active infection.

Assessment of Transplant and Cellular Immunotherapy Candidates

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

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

Assessment of Donors

Living solid organ donors should be counseled on strategies to prevent infection and monitored for exposures and symptoms in the 14 days prior to a scheduled transplant.[17] Living donors should undergo respiratory tract SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) testing within 3 days of donation. Deceased donors should be tested for SARS-CoV-2 infection using an RT-PCR assay of a sample taken from the upper respiratory tract within 72 hours of death; ideally, the test should be performed as close to organ recovery as possible. Deceased donors can be considered for donation if the results are negative **(BIII)**.

Lower respiratory sampling for COVID-19 testing is required for potential lung transplant donors by the United Network for Organ Sharing.[18] The Panel recommends following the guidance from medical professional organizations and assessing all potential HCT donors for exposure to COVID-19 and clinical symptoms that are compatible with COVID-19 before donation **(AIII)**. HCT donors should practice good hygiene and avoid crowded places and large group gatherings during the 28 days prior to donation.[19] Recommendations for screening for HCT donors are outlined in the ASTCT and EBMT guidelines.

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

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

Transplant Recipients With COVID-19

Solid organ transplant recipients who are receiving immunosuppressive therapy should be considered to be at increased risk for severe COVID-19.[21,22] A national survey of 88 U.S. transplant centers conducted between March 24 and 31, 2020, reported that 148 solid organ transplant recipients received a diagnosis of SARS-CoV-2 infection (69.6% were kidney recipients, 15.5% were liver recipients, 8.8% were heart recipients, and 6.1% were lung recipients).[23] COVID-19 was mild in 54% of recipients, moderate in 21% of recipients, and 25% of recipients were critically ill. Management strategies varied widely across the transplant centers, including different ways of modifying immunosuppressive therapy and the use of

different investigational therapies to treat COVID-19. Initial reports of transplant recipients who were hospitalized with COVID-19 suggest mortality rates of up to 28%.[24-28]

Risk of Graft Rejection

There are concerns that COVID-19 itself may increase the risk for acute rejection. Acute cellular rejection should not be presumed in 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.[21]

There are limited data on the incidence and clinical characteristics of SARS-CoV-2 infection in HCT and cellular immunotherapy recipients. Recent data from the Center for International Blood and Marrow Transplant Research demonstrated a mortality rate of approximately 30% within a month of COVID-19 diagnosis among a cohort of 318 HCT recipients.[29] This mortality rate was observed in both allogeneic and autologous recipients. Older age (≥50 years), male sex, and receipt of a COVID-19 diagnosis within 12 months of transplantation were associated with a higher risk of mortality among allogeneic recipients. In autologous recipients, patients with lymphoma had a higher risk of mortality than patients who had plasma cell disorder or myeloma.

A smaller study demonstrated a slightly lower mortality rate among HCT and cellular immunotherapy recipients than earlier reports. This study found that the number of comorbidities, the presence of infiltrates on initial chest imaging, and neutropenia were predictors for increased disease severity.[30] Additional factors that have been used to determine the clinical severity of other respiratory viral infections include the degree of cytopenia, the intensity of the conditioning regimen, the graft source, the degree of mismatch, and the need for further immunosuppression to manage graft-versus-host disease. Prolonged viral shedding has been described in solid organ transplant and HCT recipients; this can have implications for preventing infection and for the timing of therapeutic interventions.[31]

Treatment of COVID-19 in Transplant Recipients

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

Data from a large randomized controlled trial found that a short course of dexamethasone (6 mg once daily for up to 10 days) improved survival in hospitalized patients with COVID-19 who were mechanically ventilated or who required supplemental oxygen.[32] Tocilizumab or baricitinib used in combination with dexamethasone is recommended for some patients with severe or critical COVID-19 who exhibit rapid respiratory decompensation (see Interleukin-6 Inhibitors).[33-35] The risks and benefits of using dexamethasone in combination with tocilizumab or baricitinib in transplant recipients with COVID-19 who are receiving immunosuppressive therapy are unknown. Because dexamethasone, tocilizumab, and baricitinib are immunosuppressive agents, patients who receive these medications should be closely monitored for secondary infections.

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

A number of other investigational agents and drugs that are approved by the FDA for other indications

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

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

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

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

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

References

1. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med*. 2021;384(5):403-416. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33378609.
2. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. *N Engl J Med*. 2020;383(27):2603-2615. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33301246.
3. Food and Drug Administration. Vaccines and related biological products advisory committee meeting. 2021. Available at: https://www.fda.gov/media/146217/download.
4. Centers for Disease Control and Prevention. Current COVID-19 ACIP vaccine recommendations. 2020. Available at: https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/covid-19.html. Accessed January 6, 2021.
5. Boyarsky BJ, Werbel WA, Avery RK, et al. Antibody response to 2-dose SARS-CoV-2 mRNA vaccine series in solid organ transplant recipients. *JAMA*. 2021;325(21):2204-2206. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33950155.

6. Hallett AM, Greenberg RS, Boyarsky BJ, et al. SARS-CoV-2 messenger RNA vaccine antibody response and reactogenicity in heart and lung transplant recipients. *J Heart Lung Transplant*. 2021;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34456108.
7. Mazzola A, Todesco E, Drouin S, et al. Poor antibody response after two doses of SARS-CoV-2 vaccine in transplant recipients. *Clin Infect Dis*. 2021;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34166499.
8. Kamar N, Abravanel F, Marion O, Couat C, Izopet J, Del Bello A. Three doses of an mRNA COVID-19 vaccine in solid-organ transplant recipients. *N Engl J Med*. 2021;385(7):661-662. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34161700.
9. Werbel WA, Boyarsky BJ, Ou MT, et al. Safety and immunogenicity of a third dose of SARS-CoV-2 vaccine in solid organ transplant recipients: a case series. *Ann Intern Med*. 2021;174(9):1330-1332. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34125572.
10. Centers for Disease Control and Prevention. COVID-19 vaccine indications for patients who are immunocompromised. 2021. Available at: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/immunocompromised.html. Accessed September 16, 2021.
11. American Society of Transplantation. COVID-19 vaccine FAQ sheet. 2021. Available at: https://www.myast.org/sites/default/files/2021_08_13%20COVID%20VACCINE%20FAQ-Prof8132021_FINAL.pdf. Accessed September 16, 2021.
12. American Society of Hematology. ASH-ASTCT COVID-19 vaccination for HCT and CAR T cell recipients: frequently asked questions 2021. Available at: https://www.hematology.org/covid-19/ash-astct-covid-19-vaccination-for-hct-and-car-t-cell-recipients. Accessed September 16, 2021.
13. Ljungman P, Avetisyan G. Influenza vaccination in hematopoietic SCT recipients. *Bone Marrow Transplant*. 2008;42(10):637-641. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18724396.
14. Ram R, Hagin D, Kikozashvilli N, et al. Safety and immunogenicity of the BNT162b2 mRNA COVID-19 vaccine in patients after allogeneic HCT or CD19-based CART therapy-a single-center prospective cohort study. *Transplant Cell Ther*. 2021;27(9):788-794. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34214738.
15. Centers for Disease Control and Prevention. When you've been fully vaccinated: how to protect yourself and others. 2021. Available at: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated.html. Accessed September 16, 2021.
16. Ali H, Ngo D, Aribi A, et al. Safety and tolerability of SARS-CoV2 emergency-use authorized vaccines for allogeneic hematopoietic stem cell transplant recipients. *Transplant Cell Ther*. 2021;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34274492.
17. American Society of Transplantation. COVID-19 resources for transplant community. 2020. Available at: https://www.myast.org/covid-19-information. Accessed June 26, 2020.
18. United Network for Organ Sharing. Lower respiratory testing of all potential lung donors for SARS-CoV-2 now required. 2021. Available at: https://unos.org/news/sars-cov-2-lower-respiratory-testing-potential-lung-donors-may-27/. Accessed September 16, 2021.
19. American Society for Transplantation and Cellular Therapy. ASTCT interim patient guidelines April 20, 2020. 2020. Available at: https://www.astct.org/viewdocument/astct-interim-patient-guidelines-ap?CommunityKey=d3949d84-3440-45f4-8142-90ea05adb0e5&tab=librarydocuments. Accessed July 2, 2020.
20. Association of Organ Procurement Organizations. Information about COVID-19 (coronavirus) is being released rapidly. We will post updates as we receive them. 2020. Available at: https://www.aopo.org/information-about-covid-19-coronavirus-is-being-released-rapidly-we-will-post-updates-as-we-receive-them/. Accessed September 16, 2021.
21. Fix OK, Hameed B, Fontana RJ, et al. Clinical best practice advice for hepatology and liver transplant providers during the COVID-19 pandemic: AASLD expert panel consensus statement. *Hepatology*.

2020;72(1):287-304. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32298473.

22. Centers for Disease Control and Prevention. Underlying medical conditions associated with high risk for severe COVID-19: information for healthcare providers. 2021. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html. Accessed September 16, 2021.
23. Boyarsky BJ, Po-Yu Chiang T, Werbel WA, et al. Early impact of COVID-19 on transplant center practices and policies in the United States. *Am J Transplant*. 2020 ;20(7):1809-1818. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32282982.
24. Akalin E, Azzi Y, Bartash R, et al. COVID-19 and kidney transplantation. *N Engl J Med*. 2020;382(25):2475-2477. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32329975.
25. Pereira MR, Mohan S, Cohen DJ, et al. COVID-19 in solid organ transplant recipients: Initial report from the US epicenter. *Am J Transplant*. 2020;20(7):1800-1808. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32330343.
26. Alberici F, Delbarba E, Manenti C, et al. A single center observational study of the clinical characteristics and short-term outcome of 20 kidney transplant patients admitted for SARS-CoV2 pneumonia. *Kidney Int*. 2020;97(6):1083-1088. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32354634.
27. Montagud-Marrahi E, Cofan F, Torregrosa JV, et al. Preliminary data on outcomes of SARS-CoV-2 infection in a Spanish single center cohort of kidney recipients. *Am J Transplant*. 2020;20(10):2958-2959. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32368838.
28. Kates OS, Haydel BM, Florman SS, et al. COVID-19 in solid organ transplant: a multi-center cohort study. *Clin Infect Dis*. 2020;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32766815.
29. Sharma A, Bhatt NS, St Martin A, et al. Clinical characteristics and outcomes of COVID-19 in haematopoietic stem-cell transplantation recipients: an observational cohort study. *Lancet Haematol*. 2021;8(3):e185-e193. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33482113.
30. Shah GL, DeWolf S, Lee YJ, et al. Favorable outcomes of COVID-19 in recipients of hematopoietic cell transplantation. *J Clin Invest*. 2020;130(12):6656-6667. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32897885.
31. Aydillo T, Gonzalez-Reiche AS, Aslam S, et al. Shedding of viable SARS-CoV-2 after immunosuppressive therapy for cancer. *N Engl J Med*. 2020;383(26):2586-2588. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33259154.
32. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with COVID-19. *N Engl J Med*. 2021;384(8):693-704. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32678530.
33. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. 2021;397(10285):1637-1645. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33933206.
34. REMAP-CAP Investigators, Gordon AC, Mouncey PR, et al. Interleukin-6 receptor antagonists in critically ill patients with COVID-19. *N Engl J Med*. 2021;384(16):1491-1502. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33631065.
35. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus remdesivir for hospitalized adults with COVID-19. *N Engl J Med*. 2021;384(9):795-807. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33306283.
36. American Association for the Study of Liver Diseases. Clinical best practice advice for hepatology and liver transplant providers during the COVID-19 pandemic: AASLD expert panel consensus statement. 2021. Available at: https://www.aasld.org/sites/default/files/2021-03/AASLD-COVID19-ExpertPanelConsensusStatement-March92021.pdf. Accessed September 16, 2021.
37. Elens L, Langman LJ, Hesselink DA, et al. Pharmacologic treatment of transplant recipients infected with SARS-CoV-2: considerations regarding therapeutic drug monitoring and drug-drug interactions. *Ther Drug Monit*. 2020;42(3):360-368. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32304488.

Special Considerations in People With HIV

Last Updated: February 1, 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], sotrovimab, remdesivir, molnupiravir). However, in situations where there are logistical or supply constraints for administering these drugs, priority should be given to those with very advanced HIV (e.g., those with CD4 counts <50 cells/mm^3) **(AIII)**. See the Panel's statement on patient prioritization for outpatient therapies for details. • People with HIV who are taking ritonavir-based or cobicistat-based antiretroviral therapy (ART) can receive ritonavir-boosted nirmatrelvir to treat COVID-19 without altering or interrupting their ART (i.e., they can continue using the ritonavir or cobicistat dose that is associated with their ART in addition to the dose of ritonavir that is used with nirmatrelvir). • In people with advanced HIV and suspected or documented COVID-19, HIV-associated opportunistic infections should also be considered in the differential diagnosis of febrile illness **(AIII)**. • When starting treatment for COVID-19 in patients with HIV, clinicians should pay careful attention to potential drug-drug interactions and overlapping toxicities among COVID-19 treatments, antiretroviral (ARV) medications, antimicrobial therapies, and other medications **(AIII)**. • People with HIV should be offered the opportunity to participate in clinical trials that are evaluating agents for the prevention and treatment of SARS-CoV-2 infection. **Management of HIV** • People with HIV who develop COVID-19, including those who require hospitalization, should continue their ART and opportunistic infection treatment and prophylaxis whenever possible **(AIII)**. • Clinicians who are treating COVID-19 in people with HIV should consult an HIV specialist before adjusting or switching ARV medications **(AIII)**. • An ARV regimen should not be switched or adjusted (i.e., by adding ARV drugs to the regimen) for the purpose of preventing or treating SARS-CoV-2 infection **(AIII)**.

Summary Recommendations, continued
• Clinicians should consult an HIV specialist to determine the optimal time to initiate ART in people who present with COVID-19 and a new diagnosis of HIV.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional **Rating of Evidence:** I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

Introduction

Approximately 1.2 million people in the United States are living with HIV. Most of these individuals are in care, and many are on antiretroviral therapy (ART) and have well-controlled disease.[1] Similar to COVID-19, HIV disproportionately affects racial and ethnic minorities and people of lower socioeconomic status in the United States;[2] these demographic groups also appear to have a higher risk of poor outcomes with COVID-19. 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 (IV) remdesivir, IV sotrovimab, and molnupiravir (see Therapeutic Management of Nonhospitalized Adults With COVID-19). Drug-drug interactions are a special concern with ritonavir-boosted nirmatrelvir (see the Panel's statement on the drug-drug interactions for ritonavir-boosted nirmatrelvir). People with HIV who are taking ritonavir-based or cobicistat-based ART can receive the 5-day course of ritonavir-boosted nirmatrelvir to treat COVID-19 without altering or interrupting their ART (i.e., they can continue using the ritonavir or cobicistat dose that is associated with their ART in addition to the dose of ritonavir that is used with nirmatrelvir). Before prescribing ritonavir-boosted nirmatrelvir for a patient who is not already on a ritonavir-based or cobicistat-based regimen, clinicians should carefully review the patient's concomitant medications, including over-the-counter medicines and herbal supplements, and evaluate the potential for drug-drug interactions. Clinicians should utilize resources such as the EUA fact sheet for ritonavir-boosted nirmatrelvir and the Liverpool COVID-19 Drug Interactions website for additional guidance on identifying and managing drug-drug interactions.

In hospitalized patients, the appropriate treatment strategy depends on disease severity (see Therapeutic Management of Hospitalized Adults With COVID-19). Both tocilizumab and dexamethasone, which are recommended for some patients with severe or critical COVID-19, are immunosuppressive agents. The safety of using these drugs in immunocompromised patients, including those with advanced HIV, has not been studied. Therefore, patients with advanced HIV who are receiving these drugs should be closely monitored for secondary infections. Dexamethasone is a dose-dependent inducer of cytochrome P450 3A4 and could potentially lower the levels of certain coadministered ARV drugs. More than a single dose of dexamethasone **is not recommended** for patients who are receiving rilpivirine as part of their ARV regimen. Clinicians should consult an HIV specialist before administering dexamethasone to

these patients. It is currently unknown whether administering ≤10 days of dexamethasone impacts the clinical efficacy of other ARV drugs. Patients with HIV who are receiving dexamethasone as treatment for COVID-19 should follow up with their HIV providers to assess their virologic response.

Although some ARV drugs were studied for the prevention and treatment of COVID-19, no agents have been shown to be effective.

People with HIV should be offered the opportunity to participate in clinical trials of vaccines and potential treatments for COVID-19. A variety of immunomodulatory therapies are prescribed empirically or administered as part of a clinical trial to treat severe COVID-19. The data on whether these medications are safe to use in patients with HIV are lacking. If a medication has been shown to reduce the mortality of patients with COVID-19 in the general population, it should also be used to treat COVID-19 in patients with HIV, unless data indicate that the medication is not safe or effective in this population.

Managing HIV in People With COVID-19

Whenever possible, ART and opportunistic infection prophylaxis should be continued in a patient with HIV who develops COVID-19, including in those who require hospitalization **(AIII)**. Treatment interruption may lead to rebound viremia, and, in some cases, the emergence of drug resistance. If the appropriate ARV drugs are not on the hospital's formulary, administer medications from the patient's home supplies, if available.

Clinicians who are treating COVID-19 in people with HIV should consult an HIV specialist before adjusting or switching a patient's ARV medications. An ARV regimen should not be switched or adjusted (i.e., by adding ARV drugs to the regimen) for the purpose of preventing or treating SARS-CoV-2 infection **(AIII)**. Many drugs, including some ARV agents (e.g., lopinavir/ritonavir, boosted darunavir, tenofovir disoproxil fumarate/emtricitabine), have been or are being evaluated in clinical trials or are prescribed off-label to treat or prevent SARS-CoV-2 infection. To date, lopinavir/ritonavir and darunavir/cobicistat have not been found to be effective (see Lopinavir/Ritonavir and Other HIV Protease Inhibitors).[33,34] Two retrospective studies have suggested that tenofovir disoproxil fumarate/emtricitabine may play a role in preventing SARS-CoV-2 acquisition or hospitalization or death associated with COVID-19; however, the significance of these findings is unclear, as neither study adequately controlled for confounding variables such as age and comorbidities.[12,32]

For patients who are taking an investigational ARV medication as part of their ARV regimen, arrangements should be made with the investigational study team to continue the medication, if possible.

For critically ill patients who require tube feeding, some ARV medications are available in liquid formulations, and some ARV pills may be crushed. Clinicians should consult an HIV specialist and/or pharmacist to assess the best way to continue an effective ARV regimen for a patient with a feeding tube. Information may be available in the drug product label or in this document from Toronto General 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.

References

1. Harris NS, Johnson AS, Huang YA, et al. Vital signs: status of human immunodeficiency virus testing, viral suppression, and HIV preexposure prophylaxis—United States, 2013-2018. *MMWR Morb Mortal Wkly Rep*.

2019;68(48):1117-1123. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31805031.

2. Meyerowitz EA, Kim AY, Ard KL, et al. Disproportionate burden of coronavirus disease 2019 among racial minorities and those in congregate settings among a large cohort of people with HIV. *AIDS*. 2020;34(12):1781-1787. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32604138.
3. Centers for Disease Control and Prevention. COVID-19 information for specific groups of people. 2021. Available at: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/index.html. Accessed January 24, 2022.
4. Gervasoni C, Meraviglia P, Riva A, et al. Clinical features and outcomes of patients with human immunodeficiency virus with COVID-19. *Clin Infect Dis*. 2020;71(16):2276-2278. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32407467.
5. Harter G, Spinner CD, Roider J, et al. COVID-19 in people living with human immunodeficiency virus: a case series of 33 patients. *Infection*. 2020;48(5):681-686. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32394344.
6. Karmen-Tuohy S, Carlucci PM, Zervou FN, et al. Outcomes among HIV-positive patients hospitalized with COVID-19. *J Acquir Immune Defic Syndr*. 2020;85(1):6-10. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32568770.
7. Patel VV, Felsen UR, Fisher M, et al. Clinical outcomes and inflammatory markers by HIV serostatus and viral suppression in a large cohort of patients hospitalized with COVID-19. *J Acquir Immune Defic Syndr*. 2021;86(2):224-230. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33433966.
8. Shalev N, Scherer M, LaSota ED, et al. Clinical characteristics and outcomes in people living with human immunodeficiency virus hospitalized for coronavirus disease 2019. *Clin Infect Dis*. 2020;71(16):2294-2297. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32472138.
9. Sigel K, Swartz T, Golden E, et al. Coronavirus 2019 and people living with human immunodeficiency virus: outcomes for hospitalized patients in New York City. *Clin Infect Dis*. 2020;71(11):2933-2938. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32594164.
10. Stoeckle K, Johnston CD, Jannat-Khah DP, et al. COVID-19 in hospitalized adults with HIV. *Open Forum Infect Dis*. 2020;7(8):ofaa327. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32864388.
11. Vizcarra P, Perez-Elias MJ, Quereda C, et al. Description of COVID-19 in HIV-infected individuals: a single-centre, prospective cohort. *Lancet HIV*. 2020;7(8):e554-e564. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32473657.
12. Western Cape Department of Health in collaboration with the National Institute for Communicable Diseases, South Africa. Risk factors for coronavirus disease 2019 (COVID-19) death in a population cohort study from the Western Cape Province, South Africa. *Clin Infect Dis*. 2021;73(7):e2005-e2015. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32860699.
13. Bhaskaran K, Rentsch CT, MacKenna B, et al. HIV infection and COVID-19 death: a population-based cohort analysis of UK primary care data and linked national death registrations within the OpenSAFELY platform. *Lancet HIV*. 2021;8(1):e24-e32. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33316211.
14. Geretti AM, Stockdale AJ, Kelly SH, et al. Outcomes of coronavirus disease 2019 (COVID-19) related hospitalization among people with human immunodeficiency virus (HIV) in the ISARIC World Health Organization (WHO) clinical characterization protocol (UK): a prospective observational study. *Clin Infect Dis*. 2021;73(7):e2095-e2106. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33095853.
15. Dandachi D, Geiger G, Montgomery MW, et al. Characteristics, comorbidities, and outcomes in a multicenter registry of patients with human immunodeficiency virus and coronavirus disease 2019. *Clin Infect Dis*. 2021;73(7):e1964-e1972. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32905581.
16. Hoffmann C, Casado JL, Harter G, et al. Immune deficiency is a risk factor for severe COVID-19 in people living with HIV. *HIV Med*. 2021;22(5):372-378. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33368966.
17. Tesoriero JM, Swain CE, Pierce JL, et al. COVID-19 outcomes among persons living with or without diagnosed HIV infection in New York State. *JAMA Netw Open*. 2021;4(2):e2037069. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33533933.

18. Sun J, Patel RC, Zheng Q, et al. COVID-19 disease severity among people with HIV infection or solid organ transplant in the United States: a nationally-representative, multicenter, observational cohort study. *medRxiv*. 2021;Preprint. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34341798.

19. Bertagnolio S, Thwin SS, Silva R, et al. Clinical characteristics and prognostic factors in people living with HIV hospitalized with COVID-19: findings from the WHO Global Clinical Platform. Presented at: International AIDS Society. 2021. Virtual. Available at: https://theprogramme.ias2021.org/Abstract/Abstract/2498.

20. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med*. 2021;384(5):403-416. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33378609.

21. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. *N Engl J Med*. 2020;383(27):2603-2615. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33301246.

22. Food and Drug Administration. Fact sheet for healthcare providers administering vaccine (vaccination providers): emergency use authorization (EUA) of the Janssen COVID-19 vaccine to prevent coronavirus disease 2019 (COVID-19). 2022. Available at: https://www.fda.gov/media/146304/download.

23. Levy I, Wieder-Finesod A, Litchevsky V, et al. Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in people living with HIV-1. *Clin Microbiol Infect*. 2021;27(12):1851-1855. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34438069.

24. Woldemeskel BA, Karaba AH, Garliss CC, et al. The BNT162b2 mRNA vaccine elicits robust humoral and cellular immune responses in people living with HIV. *Clin Infect Dis*. 2021;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34293114.

25. Frater J, Ewer KJ, Ogbe A, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 in HIV infection: a single-arm substudy of a Phase 2/3 clinical trial. *Lancet HIV*. 2021;8(8):e474-e485. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34153264.

26. Tan SS, Chew KL, Saw S, Jureen R, Sethi S. Cross-reactivity of SARS-CoV-2 with HIV chemiluminescent assay leading to false-positive results. *J Clin Pathol*. 2021;74(9):614. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32907911.

27. Blanco JL, Ambrosioni J, Garcia F, et al. COVID-19 in patients with HIV: clinical case series. *Lancet HIV*. 2020;7(5):e314-e316. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32304642.

28. Coleman H, Snell LB, Simons R, Douthwaite ST, Lee MJ. Coronavirus disease 2019 and Pneumocystis jirovecii pneumonia: a diagnostic dilemma in HIV. *AIDS*. 2020;34(8):1258-1260. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32501852.

29. Centers for Disease Control and Prevention. HIV surveillance report: estimated HIV incidence and prevalence in the United States 2014–2018. 2020. Available at: https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-supplemental-report-vol-25-1.pdf.

30. Kong AM, Pozen A, Anastos K, Kelvin EA, Nash D. Non-HIV comorbid conditions and polypharmacy among people living with HIV age 65 or older compared with HIV-negative individuals age 65 or older in the United States: a retrospective claims-based analysis. *AIDS Patient Care STDS*. 2019;33(3):93-103. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30844304.

31. Byrd KM, Beckwith CG, Garland JM, et al. SARS-CoV-2 and HIV coinfection: clinical experience from Rhode Island, United States. *J Int AIDS Soc*. 2020;23(7):e25573. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32657527.

32. Del Amo J, Polo R, Moreno S, et al. Incidence and severity of COVID-19 in HIV-positive persons receiving antiretroviral therapy: a cohort study. *Ann Intern Med*. 2020;173(7):536-541. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32589451.

33. Recovery Collaborative Group. Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. 2020;396(10259):1345-1352. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33031764.

34. Chen J, Xia L, Liu L, et al. Antiviral activity and safety of darunavir/cobicistat for the treatment of COVID-19. *Open Forum Infect Dis*. 2020;7(7):ofaa241. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32671131.

Influenza and COVID-19

Last Updated: October 27, 2021

Summary Recommendations

Influenza Vaccination
• People with acute COVID-19 should receive an inactivated influenza vaccine **(BIII)**. For more information on administering influenza vaccines to these patients, see Interim Guidance for Routine and Influenza Immunization Services During the COVID-19 Pandemic from the Centers for Disease Control and Prevention (CDC).
  • Clinicians should consider deferring influenza vaccination for symptomatic COVID-19 patients until these patients have completed their COVID-19 isolation period and are no longer moderately or severely ill.
  • People with SARS-CoV-2 infection who are not moderately or severely ill (including those who are asymptomatic) should seek influenza vaccination when they no longer require isolation. They can be vaccinated sooner if they are in a health care setting for other reasons.
• An influenza vaccine and a COVID-19 vaccine may be administered concurrently at different injection sites (see the recommendations from CDC and the Advisory Committee on Immunization Practices).
Diagnosis of Influenza and COVID-19 When Influenza Viruses and SARS-CoV-2 Are Cocirculating
• Only testing can distinguish between SARS-CoV-2 and influenza virus infections and identify SARS-CoV-2 and influenza virus coinfection.
• The COVID-19 Treatment Guidelines Panel (the Panel) recommends testing for both viruses in all hospitalized patients with acute respiratory illness **(AIII)**.
• The Panel recommends influenza testing in addition to SARS-CoV-2 testing in outpatients with acute respiratory illness if the results will change the clinical management strategy for the patient (e.g., administering antiviral treatment for influenza) **(BIII)**.
• Clinicians should consider testing patients for other pathogens based on their specific clinical circumstances. Additional testing is especially important for patients with influenza who have a high risk of acquiring bacterial superinfections.
• See the CDC Information for Clinicians on Influenza Virus Testing and the Infectious Diseases Society of America (IDSA) Clinical Practice Guidelines for more information.
Antiviral Treatment of Influenza When Influenza Viruses and SARS-CoV-2 Are Cocirculating
• Antiviral treatment of influenza is the same in all patients with or without SARS-CoV-2 coinfection **(AIII)**.
  • For information on using antiviral drugs to treat influenza in hospitalized and nonhospitalized patients, see the CDC and IDSA recommendations.
• The Panel recommends that hospitalized patients with suspected influenza be started on empiric treatment for influenza with oseltamivir **as soon as possible** and without waiting for influenza test results **(AIIb)**.
• Antiviral treatment for influenza can be stopped when influenza has been ruled out by the results of a nucleic acid detection assay in upper respiratory tract specimens for nonintubated patients and in both upper and lower respiratory tract specimens for intubated patients.

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

Introduction

Influenza activity in the United States during the 2021 to 2022 influenza season is difficult to predict, and activity may vary depending on location and the measures taken by individual communities to mitigate the spread of SARS-CoV-2.[1] Influenza activity worldwide has been very low since the early spring of 2020, including in the United States during the 2020 to 2021 season.[2,3] Clinicians should monitor local influenza and SARS-CoV-2 activities during influenza season to inform the evaluation and management

of patients with acute respiratory illness. This can be done by tracking local and state public health surveillance data, assessing the results of testing performed at health care facilities, and reviewing the Centers for Disease Control and Prevention (CDC) Weekly U.S. Influenza Surveillance Report.

Influenza Vaccination

For Patients With Acute COVID-19 or Those Who Are Recovering From COVID-19

The Advisory Committee on Immunization Practices (ACIP) recommends offering an influenza vaccine to all persons aged ≥6 months in the United States by the end of October.[4] People with acute COVID-19 should receive an inactivated influenza vaccine **(BIII)**.

There are currently no available data on the safety, immunogenicity, or efficacy of influenza vaccines in patients with mild COVID-19 or those who are recovering from COVID-19. Therefore, the optimal timing for influenza vaccination in these patients is unknown. The safety and efficacy of vaccinating persons who have mild illnesses from other etiologies have been documented.[5] Clinicians should consider deferring influenza vaccination for symptomatic COVID-19 patients until these patients have completed their COVID-19 isolation period and are no longer moderately or severely ill. People with SARS-CoV-2 infection who are not moderately or severely ill (including those who are asymptomatic) should seek influenza vaccination when they no longer require isolation. They can be vaccinated sooner if they are in a health care setting for other reasons (see Interim Guidance for Routine and Influenza Immunization Services During the COVID-19 Pandemic from CDC for more detailed recommendations).

It is not known whether administering dexamethasone or other immunomodulatory therapies to patients with severe COVID-19 will affect the immune response to an influenza vaccine. Nevertheless, as long as influenza viruses are circulating, people with COVID-19 should receive an influenza vaccine once they have substantially improved or recovered from COVID-19. See the influenza vaccine recommendations from CDC, ACIP, and the American Academy of Pediatrics.

Coadministration of COVID-19 Vaccines and Influenza Vaccines

Although there are currently no data on the coadministration of COVID-19 vaccines and influenza vaccines, these vaccines may be administered concurrently at different injection sites. Providers and patients should be aware of the potential for increased reactogenicity when administering both vaccines concurrently (see the recommendations from CDC and ACIP).

Clinical Presentation of Influenza Versus COVID-19

The signs and symptoms of uncomplicated, clinically mild influenza overlap with those of mild COVID-19. Ageusia and anosmia can occur with both diseases, but these symptoms are more common with COVID-19 than with influenza. Fever is not always present in patients with either disease, particularly in patients who are immunosuppressed or elderly. Complications of influenza and COVID-19 can be similar, but the onset of influenza complications and severe disease typically occurs within a week of illness onset whereas the onset of severe COVID-19 usually occurs in the second week of illness. Because of the overlap in signs and symptoms, when SARS-CoV-2 and influenza viruses are cocirculating, diagnostic testing for both viruses is needed to distinguish between SARS-CoV-2 and influenza virus and to identify coinfection in people with an acute respiratory illness. Coinfection with influenza and SARS-CoV-2 has been described in case reports and case series.[6-10]

Testing for SARS-CoV-2 and Influenza

When influenza viruses and SARS-CoV-2 are cocirculating in the community, SARS-CoV-2 testing and influenza testing should be performed in all patients who are hospitalized with an acute respiratory

illness (see Testing for SARS-CoV-2 Infection) **(AIII)**. SARS-CoV-2 testing should also be performed in outpatients with suspected COVID-19, and influenza testing can be considered if the results will change the clinical management strategy for the patient (e.g., administering antiviral treatment for influenza) **(BIII)**. Several multiplex molecular assays and multiplex antigen assays that detect SARS-CoV-2 and influenza A and B viruses have received Food and Drug Administration Emergency Use Authorizations or De Novo classifications and can provide results in 15 minutes to 8 hours using a single respiratory specimen.[11,12] For more information, see the CDC Information for Clinicians on Influenza Virus Testing and the recommendations from the Infectious Diseases Society of America (IDSA) on the use of influenza tests and the interpretation of testing results.[13]

Treating Influenza With Antiviral Agents

Antiviral treatment for influenza is the same for all patients regardless of SARS-CoV-2 coinfection **(AIII)**. When SARS-CoV-2 and influenza viruses are cocirculating in the community, patients who require hospitalization and are suspected of having either or both viral infections should receive influenza antiviral treatment with oseltamivir **as soon as possible** and without waiting for influenza testing results **(AIIb)**. Oseltamivir has no activity against SARS-CoV-2[14] or known interactions with remdesivir or other therapeutics for COVID-19. The standard dose of oseltamivir is well absorbed even in critically ill patients. For patients who cannot tolerate oral or enterically administered oseltamivir (e.g., because of gastric stasis, malabsorption, or gastrointestinal bleeding), intravenous peramivir is an option.[13] There are no data on peramivir activity against SARS-CoV-2. See the CDC Influenza Antiviral Medications: Summary for Clinicians for clinical algorithms for using antiviral agents in patients with suspected or laboratory-confirmed influenza, including pregnant people and other people who are at high risk for influenza complications. The IDSA Clinical Practice Guidelines also provide recommendations on using antiviral agents to treat influenza, and the American Academy of Pediatrics provides recommendations on the antiviral treatment of influenza in children.

When the result of an influenza nucleic acid detection assay from an upper respiratory tract specimen is negative in a patient who is receiving antiviral treatment for influenza:

- *In a patient who is not intubated:* Antiviral treatment for influenza can be stopped.
- *In a patient who is intubated:* Antiviral treatment for influenza should be continued, and if a lower respiratory tract specimen (e.g., endotracheal aspirate) can be safely obtained, it should be tested using an influenza nucleic acid detection assay. If the lower respiratory tract specimen is also negative, influenza antiviral treatment can be stopped.

COVID-19 Treatment Considerations for Hospitalized Patients With Suspected or Confirmed Influenza Virus Coinfection

- Corticosteroids, which are used for the treatment of patients with severe COVID-19, may prolong influenza viral replication and viral RNA detection and may be associated with poor outcomes for influenza.[13,15] Currently, no data are available on the use of corticosteroids in patients with SARS-CoV-2 and influenza virus coinfection. However, because dexamethasone has demonstrated substantial benefits for patients with COVID-19 who require supplemental oxygen, the benefits of using corticosteroids in patients with severe SARS-CoV-2 and influenza virus coinfection likely outweigh any potential harms.
- Remdesivir does not have activity against influenza viruses. There are no known drug interactions between remdesivir and oseltamivir. Therefore, remdesivir may be used safely when indicated in patients with COVID-19 and suspected or laboratory-confirmed influenza who are receiving oseltamivir treatment.

- Although severe influenza may be associated with a dysregulated innate immune response, there are no data on the use of immunomodulatory therapies, such as interleukin-6 inhibitors (e.g., tocilizumab, sarilumab) or Janus Kinase inhibitors (e.g., baricitinib, tofacitinib), for the treatment of severe influenza. There are also no data on the effect these therapies may have on influenza viral replication. Because these immunomodulators have demonstrated a clinical benefit in certain COVID-19 patients, clinicians should consider engaging in a shared decision-making process on use of these drugs with patients who have been diagnosed with COVID-19 and who have suspected or laboratory-confirmed influenza.
- The co-occurrence of community-acquired secondary bacterial pneumonia and COVID-19 appears to be infrequent and may be more common in people who also have influenza; however, this inference is based on limited data.[16-18] Typical bacterial causes of community-acquired pneumonia with severe influenza are *Staphylococcus aureus* (methicillin-resistant *S. aureus* [MRSA] and methicillin-susceptible *S. aureus* [MSSA]), *Streptococcus pneumoniae*, and group A *Streptococcus*.[13]
- Patients with COVID-19 who develop new respiratory symptoms with or without fever or respiratory distress and who do not have a clear diagnosis should be evaluated for the possibility of nosocomial influenza.

References

1. Qi Y, Shaman J, Pei S. Quantifying the impact of COVID-19 non-pharmaceutical interventions on influenza transmission in the United States. *J Infect Dis*. 2021;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34551108.
2. World Health Organization. Review of global influenza circulation, late 2019 to 2020, and the impact of the COVID-19 pandemic on influenza circulation. *Wkly Epidemiol Rec*. 2021;96(25):241-264. Available at: https://apps.who.int/iris/handle/10665/341995.
3. Olsen SJ, Winn AK, Budd AP, et al. Changes in influenza and other respiratory virus activity during the COVID-19 pandemic—United States, 2020–2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(29):1013-1019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34292924.
4. Grohskopf LA, Alyanak E, Ferdinands JM, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices, United States, 2021-22 influenza season. *MMWR Recomm Rep*. 2021;70(5):1-28. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34448800.
5. Centers for Disease Control and Prevention. Contraindications and precautions. General best practice guidelines for immunization: best practices guidance of the advisory committee on immunization practices (ACIP). 2020. Available at: https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html. Accessed October 16, 2021.
6. Hashemi SA, Safamanesh S, Ghasemzadeh-Moghaddam H, Ghafouri M, Azimian A. High prevalence of SARS-CoV-2 and influenza A virus (H1N1) coinfection in dead patients in Northeastern Iran. *J Med Virol*. 2021;93(2):1008-1012. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32720703.
7. Huang BR, Lin YL, Wan CK, et al. Co-infection of influenza B virus and SARS-CoV-2: a case report from Taiwan. *J Microbiol Immunol Infect*. 2021;54(2):336-338. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32646801.
8. Yue H, Zhang M, Xing L, et al. The epidemiology and clinical characteristics of co-infection of SARS-CoV-2 and influenza viruses in patients during COVID-19 outbreak. *J Med Virol*. 2020;92(11):2870-2873. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32530499.
9. Cuadrado-Payan E, Montagud-Marrahi E, Torres-Elorza M, et al. SARS-CoV-2 and influenza virus co-infection. *Lancet*. 2020;395(10236):e84. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32423586.

10. Wu X, Cai Y, Huang X, et al. Co-infection with SARS-CoV-2 and influenza A virus in patient with pneumonia, China. *Emerg Infect Dis*. 2020;26(6):1324-1326. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32160148.

11. Food and Drug Administration. In vitro diagnostic EUAs—molecular diagnostic tests for SARS-CoV-2. 2021. Available at: https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/in-vitro-diagnostics-euas-molecular-diagnostic-tests-sars-cov-2. Accessed October 21, 2021.

12. Food and Drug Administration. In vitro diagnostic EUAs—antigen diagnostic tests for SARS-CoV-2. 2021. Available at: https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/in-vitro-diagnostics-euas-antigen-diagnostic-tests-sars-cov-2. Accessed October 21, 2021.

13. Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical practice guidelines by the Infectious Diseases Society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza. *Clin Infect Dis*. 2019;68(6):e1-e47. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30566567.

14. Choy KT, Wong AY, Kaewpreedee P, et al. Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro. *Antiviral Res*. 2020;178:104786. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32251767.

15. Zhou Y, Fu X, Liu X, et al. Use of corticosteroids in influenza-associated acute respiratory distress syndrome and severe pneumonia: a systemic review and meta-analysis. *Sci Rep*. 2020;10(1):3044. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32080223.

16. Vaughn VM, Gandhi T, Petty LA, et al. Empiric antibacterial therapy and community-onset bacterial co-infection in patients hospitalized with COVID-19: a multi-hospital cohort study. *Clin Infect Dis*. 2021;72(10):e533-e541. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32820807.

17. Adler H, Ball R, Fisher M, Mortimer K, Vardhan MS. Low rate of bacterial co-infection in patients with COVID-19. *Lancet Microbe*. 2020;1(2):e62. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32835331.

18. Russell CD, Fairfield CJ, Drake TM, et al. Co-infections, secondary infections, and antimicrobial use in patients hospitalised with COVID-19 during the first pandemic wave from the ISARIC WHO CCP-UK study: a multicentre, prospective cohort study. *Lancet Microbe*. 2021;2(8):e354-e365. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34100002.

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

Last Updated: February 24, 2022

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Appendix A, Table 2. COVID-19 Treatment Guidelines Panel Financial Disclosure for Companies Related to COVID-19 Treatment or Diagnostics

Last Updated: February 24, 2022

Reporting Period: April 1, 2020, to March 31, 2021

Panel Member	Financial Disclosure	
	Company	Relationship
Judith Aberg, MD	Atea Pharmaceuticals	Research Support
	Emergent BioSolutions	Research Support
	Frontier Technologies	Research Support
	Gilead Sciences	Research Support
	GlaxoSmithKline	Advisory Board, Research Support
	Janssen	Research Support
	Merck & Co.	Advisory Board, Research Support
	Pfizer	Research Support
	Regeneron	Research Support
	ViiV Healthcare	Advisory Board, Research Support
Adaora Adimora, MD, MPH	Merck & Co.	Advisory Board, Consultant, Research Support
Jason Baker, MD, MS	Gilead Sciences	Research Support
	Humanigen	Research Support
Lisa Baumann Kreuziger, MD, MS	3M	Stockholder, Spouse Is Employee
	Versiti	Employee
Roger Bedimo, MD, MS	Merck & Co.	Advisory Board
	ViiV Healthcare	Advisory Board
Pamela S. Belperio, PharmD	None	N/A
John T. Brooks, MD	None	N/A
Timothy Burgess, MD	AstraZeneca	Research Support
Danielle M. Campbell, MPH	Gilead Sciences	Advisory Board
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
	Merck & Co.	Consultant, Research Support
	ViiV Healthcare	Research Support
Demetre Daskalakis, MD, MPH	None	N/A
Richard T. Davey, Jr., MD	None	N/A
Laurie K. Doepel, BA	None	N/A
Amy L. Dzierba, PharmD	None	N/A
Derek Eisnor, MD	None	N/A
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Panel Member	Financial Disclosure	
	Company	Relationship
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Rajesh Gandhi, MD	None	N/A
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	Merck & Co.	Advisory Board
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	UCB	Advisory Board
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	Cerecor	Consultant
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Carl Hinkson, MSRC	None	N/A
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Marla J. Keller, MD	None	N/A
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Arthur Kim, MD	None	N/A
Safia Kuriakose, PharmD	None	N/A
H. Clifford Lane, MD	None	N/A
Jeffrey L. Lennox, MD	ViiV Healthcare	Research Support
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	Regeneron Pharmaceuticals	Consultant
	Sanofi	Consultant
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	Beckman Coulter	Consultant
	Genentech	Data and Safety Monitoring Board Chair/Member
	Grifols	Research Grants Review Panel
	Regeneron	Consultant
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Panel Member	Financial Disclosure	
	Company	Relationship
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	Bristol Myers Squibb	Event Adjudication
	Gilead Sciences	Research Support
	Vir Biotechnology	Advisory Board, Stockholder
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Steven Q. Simpson, MD	None	N/A
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Pablo Tebas, MD	Inovio Pharmaceuticals	Research Support
Phyllis Tien, MD, MSc	Eli Lilly and Company	Research Support
	Merck & Co.	Research Support
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	Ansun BioPharma	Research Support
	Kyorin Pharmaceutical Co.	Advisory Board
Kevin C. Wilson, MD	None	N/A
Jinoos Yazdany, MD, MPH	AstraZeneca	Consultant, Research Support
	Aurinia	Consultant
	Bristol Myers Squibb	Research Support
	Eli Lilly and Company	Consultant
	Gilead Sciences	Research Support
	Pfizer	Consultant