

COMITÊ CIENTÍFICO DE APOIO AO ENFRENTAMENTO À PANDEMIA COVID-19

GOVERNO DO ESTADO DO RIO GRANDE DO SUL



INFORMAÇÕES ATUAIS SOBRE TRATAMENTOS FARMACOLÓGICOS PARA COVID-19 COM BASE EM DECISÕES E INFORMES DE AGÊNCIAS SANITÁRIAS

ATUALIZADO EM 21 DE ABRIL DE 2021.

ATENÇÃO: Esta nota não é sugestão de protocolos de tratamento médico por parte deste comitê científico

Tendo em vista a necessidade de esclarecimentos a respeito do uso adequado de tratamentos farmacológicos para prevenção ou tratamento da COVID-19, as principais agências reguladoras nacional e internacionais do setor de saúde, incluindo - Agência Nacional de Vigilância Sanitária, ANVISA, Brasil; *Food and Drug Administration*, FDA, EUA; *National Institutes of Health*, NIH, EUA; *European Medicines Agency*, EMA, União Europeia; e Organização Mundial de Saúde, OMS - vem elaborando **orientações, com base nas melhores evidências científicas disponíveis até o momento.**

A agência regulatória para alimentos e fármacos dos EUA (FDA), além dos Institutos Nacionais de Saúde (NIH), aprovaram e recomendam o uso do fármaco antiviral **remdesivir** para pacientes com COVID-19 que necessitam hospitalização [1, 2]. **Até o momento, o remdesivir é o único medicamento antiviral não-biológico aprovado por agências regulatórias** para o tratamento de pacientes com COVID-19 [1-3].

De acordo com OMS e NIH, o corticoide dexametasona tem sido associado com desfechos mais favoráveis em pacientes com doença moderada a grave, por exemplo contribuindo para o aumento da sobrevivência de pacientes com COVID-19 hospitalizados que requerem oxigênio suplementar, especialmente em pacientes que necessitam ventilação mecânica [1, 4].

Além disso, é indicado o uso de alguns medicamentos biológicos, especificamente alguns anticorpos monoclonais, no tratamento de pacientes com COVID-19 [1, 5]. Assim, no último dia 20 de abril, a ANVISA aprovou a **autorização para uso emergencial** dos anticorpos monoclonais **casirivimabe** e **imdevimabe**, administrados em conjunto, por via intravenosa e em ambiente hospitalar, no tratamento da Covid-19. A indicação é específica para pacientes de 12 anos ou mais, com quadros leves e moderados da doença, com infecção por Sars-CoV-2 confirmada por laboratório, e que possuem alto risco de progredir para formas graves da doença [6]. O uso de **casirivimabe** e **imdevimabe** nessas condições também está aprovado pelo FDA [7, 8] e pela EMA [9].

As agências internacionais **não indicam, até o momento**, uso de cloroquina ou hidroxicloroquina em qualquer cenário do manejo da COVID-19, ou de formulações com os antivirais lopinavir e ritonavir em pacientes com COVID-19. [1-5, 10, 11].

Essas agências também **não recomendam, até o momento**, o uso de ivermectina para prevenção ou tratamento de COVID-19, a não ser no contexto de estudos clínicos randomizados, e há alerta para os riscos do uso desse fármaco em altas doses [12-14].

Cabe destacar que, especificamente no Brasil, **de acordo com a ANVISA**, no que se refere a cloroquina, hidroxicloroquina e ivermectina, não existem estudos, **até o momento**, que comprovam o uso desses medicamentos para o tratamento da COVID-19. Portanto, não há recomendação, no momento, para a sua utilização em pacientes infectados ou como forma de prevenção à contaminação pelo novo coronavírus [10, 12].

Estas evidências dependem da evolução do conhecimento científico e a cada momento de decisão elas devem ser revisadas.

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Coronavirus Disease 2019 (COVID-19) Treatment Guidelines

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

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

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What's New in the Guidelines

Last Updated: April 21, 2021

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

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

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

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

April 21, 2021

New Sections of the Guidelines

[Outpatient Management of Acute COVID-19](#)

In this section, the Panel provides recommendations for screening, triage, and therapeutic management of patients with mild to moderate COVID-19 who do not require hospitalization. This section also provides recommendations for managing patients with COVID-19 after they are discharged from the emergency department or the hospital.

[Colchicine](#)

Based on the results of a large, randomized, placebo-controlled trial in outpatients with COVID-19, the Panel has determined that there are insufficient data to recommend either for or against the use of colchicine in nonhospitalized patients with COVID-19. The Panel **recommends against** the use of colchicine in hospitalized patients, except in a clinical trial (**AIII**).

[Fluvoxamine](#)

Based on the results of a small randomized controlled trial and an observational study, the Panel has determined that there are insufficient data to recommend either for or against the use of fluvoxamine for the treatment of COVID-19.

Key Updates to the Guidelines

[Therapeutic Management of Adults With COVID-19](#)

This section has been updated to incorporate recommendations for when to use combination anti-SARS-CoV-2 monoclonal antibodies and tocilizumab (in combination with dexamethasone) in certain patients with COVID-19. This section also includes a detailed discussion of the rationale behind these recommendations.

[Overview of COVID-19](#)

A new subsection has been added to discuss the emerging information on SARS-CoV-2 variants of concern.

[Clinical Spectrum of SARS-CoV-2 Infection](#)

A new subsection describes reports of SARS-CoV-2 reinfection in individuals who had previously documented COVID-19. The discussion on patients who experience persistent symptoms or organ

dysfunction after acute COVID-19 has also been updated.

[Anti-SARS-CoV-2 Monoclonal Antibodies](#)

This section now incorporates information and recommendations from the Panel’s Statement on the Emergency Use Authorization of Anti-SARS-CoV-2 Monoclonal Antibodies for the Treatment of COVID-19 that was released on April 8, 2021. This section also includes information on the various reported SARS-CoV-2 variants and the potential impact of mutations on in vitro susceptibility to different anti-SARS-CoV-2 monoclonal antibodies.

[Convalescent Plasma](#)

High-titer convalescent plasma is available through a Food and Drug Administration Emergency Use Authorization for the treatment of certain hospitalized patients with COVID-19. This section has been updated to include new recommendations regarding the use of convalescent plasma in hospitalized patients with COVID-19 (including those who have impaired humoral immunity) and in nonhospitalized patients with COVID-19. A new [clinical data table](#) summarizes the results from several randomized clinical trials and retrospective cohort studies of convalescent plasma use in patients with COVID-19.

[Interleukin-6 Inhibitors \(With Focus on Tocilizumab\)](#)

This section has been updated to incorporate and expand on the Panel’s statements on the use of tocilizumab for the treatment of COVID-19 that were released on February 3 and March 5, 2021. This section includes considerations for using tocilizumab in combination with dexamethasone in certain hospitalized patients who are exhibiting rapid respiratory decompensation due to COVID-19. A new [clinical data table](#) summarizes the results from key studies of tocilizumab and sarilumab use in patients with COVID-19 that have had the greatest impact on the Panel’s recommendations.

[Special Considerations in Children](#)

This section now includes expanded discussions on treatment considerations for children with acute COVID-19. Additions to the section include updated information on the epidemiology and risk factors for COVID-19 in children, vertical transmission of SARS-CoV-2 infection, and multisystem inflammatory syndrome in children (MIS-C).

Other Updates to the Guidelines

The following sections have been updated to include recommendations and special considerations for SARS-CoV-2 vaccination in specific populations:

- [Special Considerations in Adults and Children With Cancer](#)
- [Special Considerations in Persons with HIV](#)
- [Special Considerations in Solid Organ Transplant, Hematopoietic Stem Cell Transplant, and Cellular Therapy Candidates, Donors, and Recipients](#)

The information in the following sections has also been updated:

- [Testing for SARS-CoV-2 Infection](#)
- [Prevention and Prophylaxis of SARS-CoV-2 Infection](#)
- [Oxygenation and Ventilation](#)
- [Remdesivir](#)
- [Vitamin C](#)
- [Vitamin D](#)
- [Zinc](#)
- [Considerations for Certain Concomitant Medications in Patients With COVID-19](#)

Introduction

Last Updated: February 11, 2021

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

Panel Composition

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

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

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

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

Development of the Guidelines

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

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

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

Method of Synthesizing Data and Formulating Recommendations

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

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

Table 1. Recommendation Rating Scheme

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

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

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

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

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

Evolving Knowledge on Treatment for COVID-19

Currently, remdesivir, an antiviral agent, is the only Food and Drug Administration-approved drug for the treatment of COVID-19. An array of drugs approved for other indications and multiple investigational agents are being studied for the treatment of COVID-19 in clinical trials around the globe. These trials can be accessed at [ClinicalTrials.gov](https://www.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: April 21, 2021

Epidemiology

The COVID-19 pandemic has exploded since cases were first reported in China in December 2019. As of April 19, 2021, more than 141 million cases of COVID-19—caused by SARS-CoV-2 infection—have been reported globally, including more than 3 million deaths.¹

Individuals of all ages are at risk for infection and severe disease. However, the probability of serious COVID-19 disease is higher in people aged ≥ 60 years, those living in a nursing home or long-term care facility, and those with chronic medical conditions. In an analysis of more than 1.3 million laboratory-confirmed cases that were reported in the United States between January and May 2020, 14% of patients required hospitalization, 2% were admitted to the intensive care unit, and 5% died.² The percentage of patients who died was 12 times higher (19.5% vs. 1.6%) and the percentage of patients who were hospitalized was six times higher (45.4% vs. 7.6%) in those with reported medical conditions than in those without medical conditions. The mortality rate was highest in those aged >70 years, regardless of the presence of chronic medical conditions. Among those with available data on health conditions, 32% had cardiovascular disease, 30% had diabetes, and 18% had chronic lung disease. Other conditions that may lead to a high risk for severe COVID-19 include cancer, kidney disease, obesity, sickle cell disease, and other immunocompromising conditions. Transplant recipients and pregnant people are also at a higher risk of severe COVID-19.³⁻¹⁰

Emerging data from the United States suggest that racial and ethnic minorities experience higher rates of COVID-19 and subsequent hospitalization and death.¹¹⁻¹⁵ However, surveillance data that include race and ethnicity are not available for most reported cases of COVID-19 in the United States.^{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 of Concern

Like other RNA viruses, SARS-CoV-2 is constantly evolving through random mutations. Any 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 lead to an increased risk of reinfection or decreased efficacy of vaccines.¹⁸ There is already evidence that some SARS-CoV-2 variants have reduced susceptibility to plasma from people who were previously infected or immunized, as well as to select monoclonal antibodies that are being considered for prevention and treatment.¹⁹

Since December 2020, several variants of concern have been identified. There is emerging evidence that the B.1.1.7 variant first seen in the United Kingdom is more infectious than earlier variants and may be more virulent.²⁰⁻²² It has become the predominant variant in the United Kingdom, and it continues to spread across the globe, including throughout many regions of the United States. The B.1.351 variant that was originally identified in South Africa is now the predominant variant in that region and has spread to many other countries, including the United States. The P.1 variant was originally identified

in Manaus, Brazil, and has now been identified in the United States. Other variants that have emerged in the United States are receiving attention, such as the B.1.427/B.1.429 variants that are circulating throughout California and the B.1.526 variant reported in New York.

The data on the emergence, spread, and clinical relevance of these new variants is rapidly evolving; this is especially true for research on how variants might affect transmission rates, disease progression, vaccine development, and the efficacy of current therapeutics. Because the research on variants of concern is moving quickly, websites such as the Centers for Disease Control and Prevention's [National Genomic Surveillance Dashboard](#) and [CoVariants.org](#) provide regular updates on the data for SARS-CoV-2 variants. The COVID-19 Treatment Guidelines Panel will review 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.^{6,23,24} The spectrum of illness can range from asymptomatic infection to severe pneumonia with acute respiratory distress syndrome and death. Among 72,314 persons with COVID-19 in China, 81% of cases were reported to be mild (defined in this study as no pneumonia or mild pneumonia), 14% were severe (defined as dyspnea, respiratory frequency ≥ 30 breaths/min, oxygen saturation [SpO₂] $\leq 93\%$, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen [PaO₂/FiO₂] < 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).²⁵ 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 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-19.²⁶ Imaging may be normal early in infection and can be abnormal in the absence of symptoms.²⁶

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

While COVID-19 is primarily a pulmonary disease, emerging data suggest that it also leads to cardiac,^{27,28} dermatologic,²⁹ hematologic,³⁰ hepatic,³¹ neurologic,^{32,33} renal,^{34,35} and other complications. Thromboembolic events also occur in patients with COVID-19, with the highest risk occurring in critically ill patients.³⁶

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).^{37,38} Please see [Special Considerations in Children](#) for more information.

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Testing for SARS-CoV-2 Infection

Last Updated: April 21, 2021

Summary Recommendations
<ul style="list-style-type: none">• To diagnose acute infection of SARS-CoV-2, the COVID-19 Treatment Guidelines Panel (the Panel) recommends using a nucleic acid amplification test (NAAT) with a sample collected from the upper respiratory tract (i.e., a nasopharyngeal, nasal, or oropharyngeal specimen) (AIII).• For intubated and mechanically ventilated adults who are suspected to have COVID-19 but who do not have a confirmed diagnosis:<ul style="list-style-type: none">• The Panel recommends obtaining lower respiratory tract samples to establish a diagnosis of COVID-19 if an initial upper respiratory tract sample is negative (BII).• The Panel recommends obtaining endotracheal aspirates over bronchial wash or bronchoalveolar lavage samples when collecting lower respiratory tract samples to establish a diagnosis of COVID-19 (BII).• A NAAT should not be repeated in an asymptomatic person within 90 days of a previous SARS-CoV-2 infection, even if the person has had a significant exposure to SARS-CoV-2 (AIII).• SARS-CoV-2 reinfection has been reported in people who have received an initial diagnosis of infection; therefore, a NAAT should be considered for persons who have recovered from a previous infection and who present with symptoms that are compatible with SARS-CoV-2 infection if there is no alternative diagnosis (BIII).• The Panel recommends against the use of serologic (i.e., antibody) testing as the sole basis for diagnosis of acute SARS-CoV-2 infection (AIII).• The Panel recommends against the use of serologic (i.e., antibody) testing to determine whether a person is immune to SARS-CoV-2 infection (AIII).
Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

Diagnostic Testing for SARS-CoV-2 Infection

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

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

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

Some tests that have received EUAs allow for self-collection of specimens at home, but these specimens

must be sent to a laboratory for processing. In addition, some tests allow trained personnel to collect and test specimens in nonclinical settings, such as in the home or in nursing or assisted living facilities. This allows real-time antigen results to be obtained on site.

Nucleic Acid Amplification Testing for SARS-CoV-2 Infection

Reverse transcriptase polymerase chain reaction (RT-PCR)-based diagnostic tests (which detect viral nucleic acids) are considered the gold standard for detecting current SARS-CoV-2 infection. More recently, NAATs have included a variety of additional platforms (e.g., reverse transcriptase loop-mediated isothermal amplification [RT-LAMP]). Clinically, there may be a window period of up to 5 days after exposure before viral nucleic acids can be detected. Diagnostically, some NAATs may produce false negative results if a mutation occurs in the part of the virus' genome that is assessed by that test.³ The FDA monitors the potential effects of SARS-CoV-2 genetic variations on NAAT results and issues updates when specific variations could affect the performance of NAATs that have received EUAs. Generally, false negative results are more likely to occur when using NAATs that rely on only one genetic target. Therefore, a single negative test result does not exclude the possibility of SARS-CoV-2 infection in people who have a high likelihood of infection based on their exposure history and/or their clinical presentation.⁴

Many commercial NAATs that use RT-PCR rely on multiple targets to detect the virus, such that even if a mutation impacts one of the targets, the other RT-PCR targets will still work.⁵ NAATs that use multiple targets are less likely to be impacted by an increased prevalence of genetic variants. In fact, because each of these tests target multiple locations on the virus' genome, they can be helpful in identifying new genetic variants before they become widespread in the population. For example, the B.1.1.7 variant that has been associated with increased transmission carries many mutations, including a double deletion at positions 69 and 70 on the spike protein gene (S-gene). This mutation appears to impact the detection of the S-gene but does not impact other genetic targets in certain NAATs. If COVID-19 is still suspected after a patient receives a negative test result, clinicians should consider repeating testing; ideally, they should use a NAAT with different genetic targets.³

SARS-CoV-2 poses several diagnostic challenges, including potentially discordant shedding of virus from the upper versus the lower respiratory tract. However, due to the high specificity of NAATs, a positive result on a NAAT of an upper respiratory tract sample from a patient with recent onset of SARS-CoV-2-compatible symptoms is sufficient to diagnose COVID-19. In patients with COVID-19, severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS), lower respiratory tract specimens have a higher viral load and thus a higher yield than upper respiratory tract specimens.⁶⁻¹² For intubated or mechanically ventilated patients with clinical signs and symptoms that are consistent with COVID-19 pneumonia, the COVID-19 Treatment Guidelines Panel (the Panel) recommends obtaining lower respiratory tract samples to establish a diagnosis of COVID-19 if an initial upper respiratory tract sample is negative (**BII**). The Panel recommends obtaining endotracheal aspirates over bronchial wash or bronchoalveolar lavage (BAL) samples when collecting lower respiratory tract samples to establish a diagnosis of COVID-19 (**BII**).

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

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

NAATs can detect SARS-CoV-2 RNA in specimens obtained weeks to months after the onset of COVID-19 symptoms.^{13,14} However, the likelihood of recovering replication-competent virus >10 days from the onset of symptoms in those with mild disease and >20 days in those with severe disease is very low.^{15,16} Furthermore, both virologic studies and contact tracing of high-risk contacts show a low risk for SARS-CoV-2 transmission after these intervals.^{17,18} Based on these results, the [Centers for Disease Control and Prevention \(CDC\)](#) recommends that NAATs should not be repeated in asymptomatic persons within 90 days of a previous SARS-CoV-2 infection, even if the person has had a significant exposure to SARS-CoV-2 (**AIII**).¹⁹ If there are concerns that an immunocompromised health care worker may still be infectious >20 days from the onset of SARS-CoV-2 infection, consultation with local employee health services regarding return-to-work testing policies is advised.

SARS-CoV-2 reinfection has been reported in people who have received an initial diagnosis of infection; therefore, a NAAT should be considered for persons who have recovered from a previous infection and who present with symptoms that are compatible with SARS-CoV-2 infection if there is no alternative diagnosis (**BIII**). However, it should be noted that persons infected with SARS-CoV-2 may have a negative result on an initial NAAT and then have a positive result on a subsequent test due to intermittent detection of viral RNA and not due to reinfection.¹³ When the results for an initial and a subsequent test are positive, comparative viral sequence data from both tests are needed to distinguish between the persistent presence of viral fragments and reinfection. In the absence of viral sequence data, the cycle threshold (Ct) value from a positive NAAT result may provide information about whether a newly detected infection is related to the persistence of viral fragments or to reinfection. The Ct value is the number of PCR cycles at which the nucleic acid target in the sample becomes detectable. In general, the Ct value is inversely related to the SARS-CoV-2 viral load. Because the clinical utility of Ct values is an area of active investigation, an expert should be consulted if these values are used to guide clinical decisions.

Antigen Testing for SARS-CoV-2 Infection

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

Increasingly, data are available to guide the use of antigen tests as screening tests to detect or exclude SARS-CoV-2 infection in asymptomatic persons, or to determine whether a person who was previously confirmed to have SARS-CoV-2 infection is still infectious. The CDC has developed an antigen testing algorithm for persons who have symptoms of COVID-19, those who are asymptomatic and have a close contact with COVID-19, and those who are asymptomatic and have no known exposure to a person with COVID-19.²⁰

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

- Incomplete adherence to the instructions for antigen test performance (e.g., reading the results outside the specified time interval or storing test cartridges/cards inappropriately)

- Test interference due to human antibodies (e.g., rheumatoid factor or other nonspecific antibodies)
- Use in communities that have a low prevalence of SARS-CoV-2 infection

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

Unlike NAATs and antigen tests for SARS-CoV-2 that detect the presence of the virus, serologic or antibody tests can detect recent or prior SARS-CoV-2 infection. Because it may take 21 days or longer after symptom onset for seroconversion to occur (i.e., the development of detectable immunoglobulin [Ig] M and/or IgG antibodies to SARS-CoV-2),²¹⁻²⁶ the Panel **does not recommend** serologic testing as the sole basis for diagnosing acute SARS-CoV-2 infection (**AIII**). Because NAATs and antigen tests for SARS-CoV-2 occasionally yield false negative results, serologic tests have been used in some settings as an additional diagnostic test for patients who are strongly suspected to have SARS-CoV-2 infection. Using a serologic test in combination with a NAAT to detect IgG or total antibodies 3 to 4 weeks after symptom onset maximizes the sensitivity and specificity to detect past infection.

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

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

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

Serologic Testing and Immunity to SARS-CoV-2 Infection

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

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

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

In communities that have a low prevalence of SARS-CoV-2 infection, the proportion of positive test results that are false positives may be quite high. In these situations, confirmatory testing using a distinct antibody assay, ideally one that uses a different antigenic target (e.g., the nucleocapsid phosphoprotein

if the first assay targeted the spike protein), can substantially improve the probability that persons with positive test results are antibody positive.

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

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

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

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

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Prevention and Prophylaxis of SARS-CoV-2 Infection

Last Updated: April 21, 2021

Summary Recommendations
<ul style="list-style-type: none">• The COVID-19 Treatment Guidelines Panel (the Panel) recommends against the use of any drugs for SARS-CoV-2 pre-exposure prophylaxis (PrEP), except in a clinical trial (AIII).• The Panel recommends against the use of hydroxychloroquine for SARS-CoV-2 post-exposure prophylaxis (PEP) (AI).• The Panel recommends against the use of other drugs for SARS-CoV-2 PEP, except in a clinical trial (AIII).• The Panel recommends that health care providers follow recommendations from the Advisory Committee on Immunization Practices when using SARS-CoV-2 vaccines (AI).
Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

General Prevention Measures

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

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

Vaccines

Currently, no SARS-CoV-2 vaccine has been approved by the Food and Drug Administration (FDA). In December 2020, the FDA issued Emergency Use Authorizations for two mRNA vaccines, BNT162b2 (Pfizer-BioNTech)⁴ and mRNA-1273 (Moderna).⁵ In February 2021, FDA issued an EUA for a human adenovirus type 26 (Ad26) vectored vaccine, Ad26.COV2.S (Johnson & Johnson/Janssen).⁶ BNT162b2 can be administered to individuals aged ≥ 16 years, whereas mRNA-1273 and Ad26.COV2.S can be given to individuals aged ≥ 18 years. Clinical trials for these vaccines in younger age groups are currently underway.

In large, placebo-controlled trials, the mRNA-1273 and BNT162b2 vaccines were 94% and 95% efficacious, respectively, in preventing symptomatic laboratory-confirmed COVID-19 after participants completed a two-dose series. The Ad26.COV2.S vaccine was 66% efficacious in preventing moderate to severe/critical laboratory-confirmed COVID-19 after a single vaccine dose. Cases of COVID-19 were confirmed by the presence of symptoms and a positive result on a SARS-CoV-2 nucleic acid amplification test (NAAT).⁶⁻⁸ All three vaccines also showed high efficacy against severe COVID-19. Local and systemic adverse events are relatively common with these vaccines, especially after the second dose. Most adverse events that occurred in vaccine trials were mild or moderate in severity (i.e.,

they did not prevent vaccinees from engaging in daily activities). There have been a few reports of severe allergic reactions following SARS-CoV-2 vaccination, including some reports of patients who experienced anaphylaxis after receiving a SARS-CoV-2 mRNA vaccine.^{6,9} Safety data continue to be collected. Certain populations, such as pregnant and lactating individuals, were not included in the initial vaccine trials. The American College of Obstetricians and Gynecologists has published interim guidance on the use of the SARS-CoV-2 mRNA vaccines in pregnant and lactating people.¹⁰

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

CDC sets the adult and childhood immunization schedules for the United States based on recommendations from the Advisory Committee on Immunization Practices (ACIP). ACIP considers disease epidemiology, burden of disease, vaccine efficacy and effectiveness, vaccine safety, the quality of the available evidence, and potential vaccination implementation issues. ACIP also sets priorities regarding who receives vaccines in the event of a shortage. ACIP COVID-19 vaccine recommendations are reviewed by CDC's Director and, if adopted, are published as official CDC recommendations in the *Morbidity and Mortality Weekly Report*.¹¹

Pre-Exposure Prophylaxis

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

Rationale

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

Clinical Trial Data

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

This double-blind, placebo-controlled, randomized trial was designed to determine whether hydroxychloroquine 600 mg per day reduced the frequency of SARS-CoV-2 infection over an 8-week period in hospital-based health care workers. The primary outcome was incidence of SARS-CoV-2 infection as determined by reverse transcriptase polymerase chain reaction (RT-PCR) assay of nasopharyngeal swabs collected at 4 and 8 weeks or the occurrence of COVID-19 symptoms.¹²

Study Population

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

Results

- The study was based on an assumed 10% infection rate for the planned inclusion of 100 participants per arm.
- Between April 9 and July 14, 2020, community SARS-CoV-2 infection rates declined. At the time of the second interim analysis (when 125 of 132 participants who provided consent were evaluable for the primary endpoint), the Data Safety Monitoring Board recommended early termination of the study for futility.
- Four participants in each group developed SARS-CoV-2 infection (positivity rate of 6.3% vs. 6.6% in the hydroxychloroquine and placebo groups, respectively; $P > 0.99$). Across the groups, six participants developed symptoms of COVID-19, but none required hospitalization.
- Serologic testing for anti-spike protein immunoglobulin (Ig) M, IgG, and nucleocapsid protein IgG demonstrated more positive results among participants in the hydroxychloroquine group (four participants [7.4%]) than in the placebo group (two participants [3.7%]), although the difference was not statistically significant ($P = 0.40$).
- Mild adverse events were more common among participants in the hydroxychloroquine group (45%) than in the placebo group (26%; $P = 0.04$). The greatest difference was the increased frequency of mild diarrhea in the hydroxychloroquine group.
- The rates of treatment discontinuation were similar in the hydroxychloroquine group (19%) and the placebo group (16%).
- There were no cardiac events in either arm and also no significant difference in the median frequency of changes in QTc between the study arms ($P = 0.98$).

Limitations

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

Interpretation

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

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

This double-blind, placebo-controlled, randomized clinical trial investigated whether hydroxychloroquine 400 mg given once- or twice-weekly for 12 weeks can prevent SARS-CoV-2 infection in health care workers at high-risk of exposure. The primary outcome was COVID-19-free survival time. Diagnosis of COVID-19 was defined as having laboratory-confirmed SARS-CoV-2 infection or having cough, shortness of breath, or difficulty breathing or having two or more of the following symptoms: fever, chills, rigors, myalgia, headache, sore throat, or new olfactory and taste disorders. COVID-19-compatible illness was included as a primary outcome even if a SARS-CoV-2 PCR test was not performed or if it was performed and the result was negative.¹³

Study Population

- The study participants had to be working in the emergency department, in the intensive care unit, on a dedicated COVID-19 hospital ward, or as a first responder; alternatively, they had to have a

job description that included regularly performing aerosol-generating procedures.

- Participants were recruited via social media platforms. Informed consent was obtained remotely, and the study drug was delivered to the participants by couriers.

Results

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

Limitations

- The study was prematurely halted due to poor enrollment; therefore, the study population was insufficient to detect differences in outcomes among the study arms.
- The study only assessed the SARS-CoV-2 inhibitory activity of two doses of hydroxychloroquine, neither of which achieved concentrations that exceeded the in vitro EC_{50} of the drug.
- Only 17.5% of the participants who met study endpoints had positive SARS-CoV-2 test results; the remainder had COVID-19-compatible symptoms without a confirmatory diagnosis.

Interpretation

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

Post-Exposure Prophylaxis

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

Rationale

Several randomized controlled trials have evaluated the use of hydroxychloroquine for SARS-CoV-2 PEP.¹⁴⁻¹⁶ None of these studies have reported any evidence of efficacy, and all showed a higher frequency of adverse events among participants who received hydroxychloroquine than among control participants. The results of some of these studies are described below.

A number of agents (e.g., anti-SARS-CoV-2 monoclonal antibodies, hyperimmune gammaglobulin, convalescent plasma, ivermectin, interferons, tenofovir with or without emtricitabine, vitamin D) are currently being investigated for SARS-CoV-2 PEP. The latest clinical trials for SARS-CoV-2 PEP can be found at [ClinicalTrials.gov](https://clinicaltrials.gov).

Clinical Trial Data

Both chloroquine and hydroxychloroquine have in vitro activity against severe acute respiratory syndrome-associated coronavirus (SARS-CoV) and SARS-CoV-2.^{17,18} A small cohort study without a control group suggested that hydroxychloroquine might reduce the risk of SARS-CoV-2 transmission to close contacts.¹⁹

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

A household-randomized, double-blind controlled trial evaluated the use of hydroxychloroquine as PEP to prevent SARS-CoV-2 infection. The study was conducted at seven institutions in the United States between March and August 2020. Participants were recruited using online advertising, social media, and referrals from hospitals, health departments, and individuals with laboratory-confirmed SARS-CoV-2 infection.¹⁴

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

Study Population

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

Results

- A total of 98 SARS-CoV-2 infections were detected during the first 14 days of follow-up, with an overall cumulative incidence of 14.3% (95% CI, 11.5% to 17%). Fifty-three events (i.e., PCR-

confirmed SARS-CoV-2 infection) occurred in the hydroxychloroquine group, and 45 events occurred in the control group (aHR 1.10; 95% CI, 0.73–1.66; $P > 0.20$)

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

Limitations

- There was an average window of 2 days between the time of the most recent exposure to the index people and the time the study drugs were administered. The lapse of time between exposure to SARS-CoV-2 and initiation of hydroxychloroquine may have affected the efficacy of the drug as PEP.
- The primary analysis excluded approximately 10% of enrolled people who were shown to have SARS-CoV-2 infection at baseline.

Interpretation

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

Double-Blind Randomized Controlled Trial of Hydroxychloroquine as Post-Exposure Prophylaxis in Contacts With High-Risk or Moderate-Risk Occupational or Household Exposures

This double-blind randomized controlled trial included 821 participants who self-enrolled in the study using an internet-based survey. Participants were randomized to receive either hydroxychloroquine (hydroxychloroquine 800 mg once, followed by hydroxychloroquine 600 mg 6 to 8 hours later, and then hydroxychloroquine 600 mg once daily for 4 additional days) or placebo. Because enrollment was done online, the study drugs were sent to participants by overnight mail, and consequently, more than 50% of the participants started the first dose of their assigned treatment 3 to 4 days after exposure to SARS-CoV-2.¹⁶

Study Population

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

Results

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

incidence of the primary outcome (symptomatic illness) between the hydroxychloroquine group and the placebo group (11.8% vs. 14.3%, respectively; $P = 0.35$).

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

Limitations

- Most participants did not start their assigned therapy until at least 3 days after exposure to SARS-CoV-2.
- Only 15% of participants who reached the primary outcome had SARS-CoV-2 infection confirmed by molecular diagnostics.
- The study participants were young (median age 40 years) and had a relatively low risk of severe COVID-19.

Interpretation

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

Cluster-Randomized Trial of SARS-CoV-2 Post-Exposure Prophylaxis With Hydroxychloroquine

This open-label, cluster-randomized trial included 2,314 asymptomatic contacts of 672 COVID-19 cases in Spain.¹⁵ Participants who were epidemiologically linked to a PCR-positive COVID-19 case were defined as study clusters (called rings). All contacts in a ring were simultaneously cluster-randomized in a 1:1 ratio to the control arm (usual care) or the intervention arm (hydroxychloroquine 800 mg once daily for 1 day, followed by hydroxychloroquine 400 mg once daily for 6 days). Participants were informed of their allocated study arm after being randomized to the intervention or control arm and signing a consent form.

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

Study Population

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

Results

- A total of 138 study participants (6.0%) developed PCR-confirmed, symptomatic SARS-CoV-2 infection. There was no statistical difference in the incidence of confirmed infection between the hydroxychloroquine and control arms (5.7% vs. 6.2%, respectively; risk ratio 0.86; 95% CI, 0.52–1.42).

- There was no statistical difference between the study arms in the incidence of either PCR-confirmed or symptomatically compatible COVID-19, which was 18.2% overall (18.7% in the hydroxychloroquine arm vs. 17.8% in the control arm; risk ratio 1.03; 95% CI, 0.77–1.38).
- There was no statistical difference between the arms in the rate of positivity for SARS-CoV-2 IgM and/or IgG (14.3% in the hydroxychloroquine arm vs. 8.7% in the control arm; risk ratio 1.57; 95% CI, 0.94–2.62).
- There were more adverse events among the hydroxychloroquine-treated participants (56.1%) than among the control participants (5.9%), although most of the adverse events were mild. Common adverse events included gastrointestinal events, nervous system disorders, myalgia, fatigue, and malaise. No serious adverse events were attributed to the study drug.

Limitations

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

Interpretation

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

Ivermectin

High concentrations of ivermectin have been shown to inhibit SARS-CoV-2 replication in vitro.^{20,21} Population data also indicate that country-wide mass use of prophylactic chemotherapy for parasitic infections, including the use of ivermectin, is associated with a lower incidence of COVID-19.²² At this time, there are limited clinical trials regarding the safety and efficacy of 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 lack of details regarding the safety and efficacy of ivermectin. The results of these trials are described below.

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.²³ An open-label, randomized controlled trial investigated ivermectin prophylaxis (plus personal protective measures [PPMs]) in health care workers (as PrEP) or in household contacts (as PEP) exposed to patients with laboratory-confirmed COVID-19. The incidence of SARS-CoV-2 infection was lower among the participants who received ivermectin than among control participants who used only PPMs. However, the study provided no data on the characteristics of the study participants, types of exposures, or how endpoints were defined.²⁴ Finally, 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.²⁵

Additional studies of ivermectin for SARS-CoV-2 are ongoing. Please see [ClinicalTrials.gov](https://clinicaltrials.gov) for the latest information.

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Clinical Spectrum of SARS-CoV-2 Infection

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Patients with SARS-CoV-2 infection can experience a range of clinical manifestations, from no symptoms to critical illness. This section of the Guidelines discusses the clinical presentation of SARS-CoV-2-infected individuals according to illness severity.

In general, adults with SARS-CoV-2 infection can be grouped into the following severity of illness categories. However, the criteria for each category may overlap or vary across clinical guidelines and clinical trials, and a patient's clinical status may change over time.

Asymptomatic or Presymptomatic Infection: Individuals who test positive for SARS-CoV-2 using a virologic test (i.e., a nucleic acid amplification test [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) $\geq 94\%$ on room air at sea level.

Severe Illness: Individuals who have $\text{SpO}_2 < 94\%$ on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) < 300 mm Hg, respiratory frequency > 30 breaths/min, or lung infiltrates $> 50\%$.

Critical Illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

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

The optimal pulmonary imaging technique has not yet been defined for people with symptomatic SARS-CoV-2 infection. Initial evaluation for these patients may include chest X-ray, ultrasound, or, if indicated, computed tomography. An electrocardiogram should be performed if indicated. Laboratory testing includes a complete blood count with differential and a metabolic profile, including liver and renal function tests. 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 individual section of the Guidelines.

In pediatric patients, radiographic abnormalities are common and, for the most part, should not be the only criteria used to determine the severity of illness. The normal values for respiratory rate also vary with age in children; thus, hypoxia 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} The availability of widespread virologic testing for SARS-CoV-2 and the development of reliable serologic assays for antibodies to the virus will help determine the true prevalence of asymptomatic and presymptomatic infection. See [Therapeutic Management of 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 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 $\text{SpO}_2 \geq 94\%$ 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 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 $\text{SpO}_2 < 94\%$ on room air at sea level, a respiratory rate > 30 breaths/min, $\text{PaO}_2/\text{FiO}_2 < 300$ mm Hg, or lung infiltrates $> 50\%$. These patients may experience rapid clinical deterioration. Oxygen therapy should be administered immediately using a nasal cannula or a high-flow oxygen device. See [Therapeutic Management of 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 Patients With COVID-19](#).

SARS-CoV-2 Reinfection

As seen with other viral infections, reinfection with SARS-CoV-2 after recovery from prior infection has been reported.¹² The true prevalence of reinfection is not known, although there are concerns that it may occur with increased frequency with the circulation of new variants.¹³ SARS-CoV-2 can often be detected from nasal swab for weeks to months after initial infection, therefore, repeat testing to evaluate for reinfection should be considered only for those who have recovered from initial infection and present with COVID-19-compatible symptoms with no obvious alternate etiology (**AIII**).¹⁴ 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).¹⁵

It has been speculated that reinfection may occur more frequently in those with 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 diagnosis of the initial infection.¹⁶ A public site posts a variety of published and unpublished reports of reinfection, noting that it has been described to occur from as early as a few weeks to many months after initial infection, and occasionally follows episodes of severe COVID-19.¹⁷ Although data are limited, there is no evidence to suggest that the treatment of highly suspected or documented SARS-CoV-2 reinfection should be different from that for initial infection as outlined in [Therapeutic Management of 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, including lack of an agreed-upon case definition and potential bias as most reports included only patients who attended post-COVID-19 clinics and no 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.^{18,19} 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.²⁰ 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.²¹

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).^{22,23}

Despite limitations of the available descriptive data related to 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.^{24,25}

CDC conducted a telephone survey of a random sample of 292 adult outpatients who had positive polymerase chain reaction results for SARS-CoV-2. Among the 274 respondents who were symptomatic at the time of testing, 35% reported not having returned to their usual state of health 2 weeks or more after testing; 26% among patients aged 18 to 34 years, 32% among those aged 35 to 49 years, and 47% among those aged ≥ 50 years.²³ 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.²⁶ 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.²⁷ Overall, 91% of the respondents were outpatients (150 with mild illness and 11 with no symptoms), and only 9.0% had moderate or severe disease requiring hospitalization. Among those reporting symptoms, 33% of the outpatients and 31% of the hospitalized patients reported at least one persistent symptom. Persistent symptoms were reported by 27% of the patients aged 18 to 39 years, 30% aged 40 to 64 years, and 43% aged ≥ 65 years. The most common persistent symptoms were loss of sense of smell or taste and fatigue (both reported by 14% of participants).

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.²⁸ An outpatient service for patients recovering from acute COVID-19 developed in Italy reported that 87% of 143 patients surveyed reported persistent symptoms at a mean of 60 days after symptom onset, with the most common symptom being fatigue (which occurred in 53.1% of these patients).²¹

Cardiopulmonary

A study from the United Kingdom reported that among 100 hospitalized patients (32 received care in the ICU and 68 received care in hospital wards only), 72% of the ICU patients and 60% of the ward patients experienced fatigue and breathlessness at 4 to 8 weeks after hospital discharge. The authors suggested that posthospital rehabilitation may be necessary for some of these patients.²⁴ 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%).²⁹ 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.³⁰ 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%).³¹ The assessment of the prevalence of cardiac abnormalities in people with post-acute COVID-19 syndrome 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.^{25,32} Younger patients have been reported to experience more psychiatric symptoms than patients aged >60 years.^{24,25} 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-19.³³⁻³⁵ 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.³⁶ However, the study authors did not report when the tests were administered in relation to the diagnosis of COVID-19.

Persistent symptoms after acute COVID-19 have also been reported in pregnant people.³⁷ 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.^{38,39} MIS-C is discussed in [Special Considerations in Children](#).

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

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Outpatient Management of Acute COVID-19

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Summary Recommendations
<p>Managing Outpatients With COVID-19</p> <ul style="list-style-type: none">• Outpatient management of acute COVID-19 should include providing supportive care, taking steps to reduce the risk of SARS-CoV-2 transmission (including isolating the patient), and advising patients on when to contact a health care provider and seek an in-person evaluation (AIII).• Patients with symptoms of COVID-19 should be triaged, when possible, via telehealth visits before receiving in-person care. Patients with dyspnea should be referred for an in-person evaluation by a health care provider and should be followed closely during the initial days after the onset of dyspnea to assess for worsening respiratory status (AIII).• Management plans should be based on a patient's vital signs, physical exam findings, risk factors for progression to severe illness, and the availability of health care resources (AIII). <p>Specific Therapy for Outpatients With Mild to Moderate COVID-19</p> <ul style="list-style-type: none">• The COVID-19 Treatment Guidelines Panel (the Panel) recommends using one of the following combination anti-SARS-CoV-2 monoclonal antibodies to treat outpatients with mild to moderate COVID-19 who are at high risk of clinical progression, as defined by the Emergency Use Authorization criteria (treatments are listed in alphabetical order):<ul style="list-style-type: none">• Bamlanivimab 700 mg plus etesevimab 1,400 mg (AIIa); or• Casirivimab 1,200 mg plus imdevimab 1,200 mg (AIIa).• The Panel recommends against the use of chloroquine or hydroxychloroquine with or without azithromycin (AI). There are insufficient data for the Panel to recommend either for or against the use of other agents for the treatment of outpatients with COVID-19.• The Panel recommends against the use of dexamethasone or other systemic glucocorticoids in outpatients in the absence of another indication (AIII). There is currently a lack of safety and efficacy data on the use of these agents in outpatients with COVID-19, and systemic glucocorticoids may cause harm in these patients.• The Panel recommends against the use of antibacterial therapy (e.g., azithromycin, doxycycline) in the absence of another indication (AIII).• 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 participating in clinical trials (AIII).
<p>Rating of Recommendations: A = Strong; B = Moderate; C = Optional</p> <p>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</p>

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 (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 amid the rising number of COVID-19 hospitalizations across the country. 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.

Outpatient Management of 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) and 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

There are limited data to inform outpatient management strategies; current strategies are based mostly on clinical experience accumulated since the beginning of the pandemic. Management of COVID-19 patients in the outpatient setting should focus on providing supportive care, taking steps to reduce the risk of SARS-CoV-2 transmission (e.g., wearing a mask, isolating the patient),^{4,5} and advising patients when to seek in-person evaluation.⁶ Supportive care includes managing symptoms (as described below), assuring 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 consideration of 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.

Criteria to Determine Whether In-Person Evaluation Is Needed

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

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

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

Clinical Considerations When Managing Patients in an Ambulatory Care Setting

Persons who have symptoms that are compatible with COVID-19 or who have been exposed to others with suspected or laboratory-confirmed COVID-19 should undergo diagnostic SARS-CoV-2 testing (see [Prevention and Prophylaxis 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 onset of dyspnea, to monitor for worsening respiratory status (**AIII**).

If an adult patient has access to a pulse oximeter at home, SpO₂ measurements can be used to help assess overall clinical status. Patients should be advised to use a pulse oximeter on warm fingers rather than cold fingers for better accuracy. Patients should inform their health care provider if the value is repeatedly below 95% at sea level. Pulse oximetry may not accurately detect occult hypoxemia, especially in Black patients.^{3,17,18} Additionally, SpO₂ readings obtained through a mobile telephone 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 risk for disease progression and 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 by 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.

Symptom Management

Symptomatic treatment includes using over-the-counter antipyretics, analgesics, and antitussives for fever, headache, myalgias, and cough. Patients with dyspnea may benefit from resting in the prone position rather than the supine position.²² Health care providers should consider educating patients about breathing exercises, as severe breathlessness may cause anxiety.²³ 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.

Therapeutic Management

The Panel continues to review the most recent clinical data to provide up-to-date treatment recommendations for clinicians who are caring for patients with COVID-19. [Therapeutic Management of Adults With COVID-19](#) includes recommendations for managing patients with varying severities of disease.

Anti-SARS-CoV-2 Monoclonal Antibodies

The Panel recommends using one of the following combination anti-SARS-CoV-2 monoclonal antibodies to treat outpatients with mild to moderate COVID-19 who are at high risk of clinical progression as defined by the Emergency Use Authorization (EUA) criteria (treatments are listed in alphabetical order):

- **Bamlanivimab 700 mg plus etesevimab 1,400 mg (AIIa); or**
- **Casirivimab 1,200 mg plus imdevimab 1,200 mg (AIIa).**

Treatment should be started as soon as possible after the patient receives a positive result on a SARS-CoV-2 antigen test or a nucleic acid amplification test and within 10 days of symptom onset. For more details on the available clinical trial data for these antibodies, see [Anti-SARS-CoV-2 Monoclonal Antibodies](#).

Two combination anti-SARS-CoV-2 monoclonal antibody products—bamlanivimab plus etesevimab and casirivimab plus imdevimab—have received EUAs from the Food and Drug Administration (FDA) for the treatment of mild to moderate COVID-19 in outpatients who are at high risk of clinical progression. In laboratory studies, some SARS-CoV-2 variants of concern or interest that harbor certain mutations have markedly reduced susceptibility to bamlanivimab and may have lower sensitivity to etesevimab and casirivimab.²⁴ Reduced in vitro susceptibility to both antibodies in a combination regimen is currently uncommon.

There are no comparative data to determine whether there are differences in clinical efficacy or safety between bamlanivimab plus etesevimab and casirivimab plus imdevimab. There are SARS-CoV-2 variants, particularly those that contain the mutation E484K, that reduce the virus' susceptibility to bamlanivimab and, to a lesser extent, casirivimab and etesevimab in vitro; however, the clinical impact of these mutations is not known. In regions where SARS-CoV-2 variants with reduced in vitro susceptibility to bamlanivimab plus etesevimab are common, some Panel members would preferentially use casirivimab plus imdevimab while acknowledging that it is not known whether in vitro susceptibility data correlate with clinical outcomes.

Vaccination with a COVID-19 vaccine should be deferred for at least 90 days in those who have received anti-SARS-CoV-2 monoclonal antibodies. This is a precautionary measure, as the antibody

treatment may interfere with vaccine-induced immune responses. In people who are vaccinated and then develop COVID-19, prior receipt of vaccine should not affect treatment decisions, including the use of and timing of treatment with monoclonal antibodies.²⁵

Other Therapeutic Agents

The Panel **recommends against** the use of **chloroquine** or **hydroxychloroquine** with or without **azithromycin** for the treatment of COVID-19 (**AI**). 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 participating in clinical trials (**AIII**).

Remdesivir

Remdesivir is currently the only drug approved by the FDA for the treatment of COVID-19. It is recommended for use in hospitalized patients who require supplemental oxygen. In some cases, a hospital bed may not be available for patients who require supplemental oxygen; for these patients, remdesivir should only be administered in health care settings that can provide a similar level of care to an inpatient hospital.

Dexamethasone

The Panel **recommends against** the use of **dexamethasone** or **other systemic glucocorticoids** to treat outpatients with mild to moderate COVID-19 (**AIII**). There is currently a lack of safety and efficacy data on the use of these agents in outpatients with COVID-19, 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**). For more information, see [Therapeutic Management of Adults With COVID-19](#). The use of dexamethasone in outpatients with severe disease is discussed below.

In hospitalized patients with COVID-19, dexamethasone was shown to reduce mortality in patients who required supplemental oxygen. There was no observed benefit of dexamethasone in hospitalized patients who did not receive oxygen support.²⁶ Outpatients with mild to moderate COVID-19 were not included in this trial; thus, the safety and efficacy of corticosteroids in this population have not been established. The Panel **recommends against** the use of **corticosteroids** in this population as there are no clinical trial data to support their use (**AIII**). Moreover, the use of corticosteroids can lead to adverse effects, such as hyperglycemia, neuropsychiatric symptoms, and secondary infections, all of which may be difficult to detect and monitor in an outpatient setting. In some cases, a hospital bed may not be available for patients who require supplemental oxygen; for these patients, clinicians can consider administering dexamethasone only if the patient is placed in a health care setting that can provide a similar level of care to an inpatient hospital.

Antithrombotic Therapy

Anticoagulants and antiplatelet therapy should not be initiated in the outpatient setting for the prevention of venous thromboembolism (VTE) or arterial thrombosis unless the patient has other indications for the therapy or is participating in a clinical trial (**AIII**). 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.

Antibacterial Therapy

The Panel **recommends against** the use of **antibacterial therapy** (e.g., **azithromycin**, **doxycycline**) for outpatient treatment of COVID-19 in the absence of another indication (**AIII**).

Concomitant Medication Management

In general, a patient's usual medication and/or supplement regimen should be continued after the diagnosis of COVID-19 (see [Considerations for Certain Concomitant Medications in Patients With COVID-19](#)). **Angiotensin-converting enzyme inhibitors, statin therapy, nonsteroidal anti-inflammatory drugs, and oral, inhaled, and intranasal corticosteroids** 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-2.²⁷ 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 associated with 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 isolated from others.

Outpatient Management of Adults With COVID-19 Following Discharge from the Emergency Department

There are no fixed criteria for hospital admission of patients with COVID-19; the criteria may vary by region and hospital facilities. Patients with severe disease are typically admitted to the hospital, but due to the high prevalence of infection and limited hospital resources, some patients with severe disease may not be admitted. 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.²⁸ 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.

In the cases where institutional resources (e.g., inpatient beds, staff members) are scarce, it may be necessary to discharge an adult patient home and provide an advanced level of home care, including supplemental oxygen (if indicated), pulse oximetry, and close follow-up. Although early discharge of those with severe disease is not generally recommended by the Panel, it is recognized that these management strategies are sometimes necessary. In these situations, some institutions are providing frequent telemedicine follow-up visits for these patients or providing a hotline for patients to speak with a clinician if 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.

Both dexamethasone and remdesivir may be appropriate treatment for some patients who are discharged from the ED but require supplemental oxygen, even though they are not hospitalized (see [Therapeutic Management of Adults With COVID-19](#)). Since remdesivir can only be administered by intravenous infusion, there may be logistical issues with providing it to an outpatient. If dexamethasone is given, it should be provided for no more than 10 days, and clinicians should consider stopping dexamethasone

when the patient no longer requires oxygen. It is important that patients on dexamethasone or other corticosteroids are counseled about potential adverse effects, including hyperglycemia and neuropsychiatric impairment. In-person visits or telehealth visits should be performed to monitor closely for toxicities and/or assist with blood glucose control.

Anticoagulants and antiplatelet therapy should not be initiated for the prevention of VTE or arterial thrombosis unless the patient has other indications for the therapy or is participating in a clinical trial (**AIII**). 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.

Outpatient Management of 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 visit 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. When possible, these individuals should receive oximetry monitoring and close follow-up through telehealth, visiting nurse services, or in-person clinic visits.

The pivotal safety and efficacy trials for remdesivir and corticosteroids stopped these treatments at the time of discharge from the hospital; therefore, these therapies are generally discontinued in patients who are discharged from an inpatient setting, even if they are receiving supplemental oxygen. Nevertheless, it is recognized that the practice of discharging inpatients who still require oxygen was likely uncommon in the pivotal trials. The data supporting the use of corticosteroids after discharge in such cases are limited, with the main concerns being the lack of monitoring for toxicities, including, but not limited to, blood glucose control and neuropsychiatric impairment. As a result, the Panel **recommends against** administering **corticosteroids** after discharge as routine practice (**BIII**). If a patient continues to receive corticosteroids after discharge, it should be for no more than a total of 10 days and only in those who are stable and have shown good tolerance to this therapy prior to discharge.

Hospitalized patients with COVID-19 should not routinely be discharged on 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 for 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-19.²⁹ 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, SpO₂ should be maintained at 95% or above at sea level; therefore, the threshold for monitoring pregnant patients in an inpatient setting may be lower than in nonpregnant patients.³⁰ In general, there are no changes to fetal monitoring recommendations in the outpatient setting, and fetal management should be similar to that provided to other pregnant patients with medical illness.³¹ 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, or 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 are insufficient pediatric data to recommend either for or against the use of anti-SARS-CoV-2 monoclonal antibody products in 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 the EUA criteria, especially those who meet more than one criterion or are aged ≥ 16 years. The Panel recommends consulting a pediatric infectious disease specialist in such cases.

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 the [Special Considerations in Children](#) section for more information on the management of children with COVID-19.

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Care of Critically Ill Adult Patients With COVID-19

Last Updated: December 17, 2020

Summary Recommendations

Infection Control

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

Hemodynamics

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

Oxygenation and Ventilation

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

improve oxygenation (**CIIa**).

- The Panel **recommends against** using awake prone positioning as a rescue therapy for refractory hypoxemia to avoid intubation in patients who otherwise meet the indications for intubation and mechanical ventilation (**AIII**).
- If intubation becomes necessary, the procedure should be performed by an experienced practitioner in a controlled setting due to the enhanced risk of severe acute respiratory syndrome coronavirus 2 exposure to health care practitioners during intubation (**AIII**).
- For mechanically ventilated adults with COVID-19 and acute respiratory distress syndrome (ARDS):
 - The Panel recommends using low tidal volume (VT) ventilation (VT 4–8 mL/kg of predicted body weight) over higher VT ventilation (VT >8 mL/kg) (**AI**).
 - The Panel recommends targeting plateau pressures of <30 cm H₂O (**AIIa**).
 - The Panel recommends using a conservative fluid strategy over a liberal fluid strategy (**BIIa**).
 - The Panel **recommends against** the routine use of inhaled nitric oxide (**AIIa**).
- For mechanically ventilated adults with COVID-19 and moderate-to-severe ARDS:
 - The Panel recommends using a higher positive end-expiratory pressure (PEEP) strategy over a lower PEEP strategy (**BIIa**).
 - For mechanically ventilated adults with COVID-19 and refractory hypoxemia despite optimized ventilation, the Panel recommends prone ventilation for 12 to 16 hours per day over no prone ventilation (**BIIa**).
- For mechanically ventilated adults with COVID-19 and moderate-to-severe ARDS:
 - The Panel recommends using, as needed, intermittent boluses of neuromuscular blocking agents (NMBA) or continuous NMBA infusion to facilitate protective lung ventilation (**BIIa**).
 - In the event of persistent patient-ventilator dyssynchrony, or in cases where a patient requires ongoing deep sedation, prone ventilation, or persistently high plateau pressures, the Panel recommends using a continuous NMBA infusion for up to 48 hours as long as patient anxiety and pain can be adequately monitored and controlled (**BIII**).
- For mechanically ventilated adults with COVID-19, severe ARDS, and hypoxemia despite optimized ventilation and other rescue strategies:
 - The Panel recommends using recruitment maneuvers rather than not using recruitment maneuvers (**CIIa**).
 - If recruitment maneuvers are used, the Panel **recommends against** using staircase (incremental PEEP) recruitment maneuvers (**AIIa**).
 - The Panel recommends using an inhaled pulmonary vasodilator as a rescue therapy; if no rapid improvement in oxygenation is observed, the treatment should be tapered off (**CIII**).

Acute Kidney Injury and Renal Replacement Therapy

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

Pharmacologic Interventions

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

Extracorporeal Membrane Oxygenation

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

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

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

General Considerations

Last Updated: 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, arrhythmias, and thromboembolic disease.¹⁶

Thromboembolic Events and COVID-19

Critically ill patients with COVID-19 have been observed to have a prothrombotic state, which is characterized by the elevation of certain biomarkers, and there is an apparent increase in the incidence of venous thromboembolic disease in this population. In some studies, thromboemboli have been diagnosed in patients who received chemical prophylaxis with heparinoids.¹⁷⁻¹⁹ Autopsy studies provide additional evidence of both thromboembolic disease and microvascular thrombosis in patients with COVID-19.²⁰ Some authors have called for routine surveillance of ICU patients for venous thromboembolism.²¹ See the [Antithrombotic Therapy in Patients with COVID-19](#) section for a more detailed discussion.

Renal and Hepatic Dysfunction Due to COVID-19

Although SARS-CoV-2 is primarily a pulmonary pathogen, renal and hepatic dysfunction are consistently described in patients with severe COVID-19.⁴ In one case series of patients with critical

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

Considerations in Children

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

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

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

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

Sedation Management in Patients With COVID-19

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

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

- A. Assess, prevent, and manage pain;
- B. Both spontaneous awakening and breathing trials;
- C. Choice of analgesia and sedation;
- D. Delirium: assess, prevent, and manage;
- E. Early mobility and exercise; *and*
- F. Family engagement and empowerment.

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

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

Post-Intensive Care Syndrome

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

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

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

Other Intensive Care Unit-Related Complications

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

Advance Care Planning and Goals of Care

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

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

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

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

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Infection Control

Last Updated: October 9, 2020

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

Recommendation

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

Rationale

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

Recommendation

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

Rationale

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

Recommendations

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

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

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

Rationale

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

Recommendations

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

Rationale

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

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Hemodynamics

Last Updated: October 9, 2020

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

COVID-19 patients who require fluid resuscitation or hemodynamic management of shock should be treated and managed for septic shock in accordance with other published guidelines, with the following exceptions.

Recommendation

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

Rationale

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

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

Recommendation

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

Rationale

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

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

Recommendation

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

Rationale

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

Additional Recommendations Based on General Principles of Critical Care

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

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Oxygenation and Ventilation

Last Updated: December 17, 2020

The COVID-19 Treatment Guidelines Panel's (the Panel's) recommendations below emphasize recommendations from the Surviving Sepsis Campaign Guidelines for [adult sepsis](#), [pediatric sepsis](#), and [COVID-19](#).

Nonmechanically Ventilated Adults With Hypoxemic Respiratory Failure

Recommendations

- For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy, the Panel recommends high-flow nasal cannula (HFNC) oxygen over noninvasive positive pressure ventilation (NIPPV) (**BIIa**).
- In the absence of an indication for endotracheal intubation, the Panel recommends a closely monitored trial of NIPPV for adults with COVID-19 and acute hypoxemic respiratory failure and for whom HFNC is not available (**BIIa**).
- For patients with persistent hypoxemia despite increasing supplemental oxygen requirements in whom endotracheal intubation is not otherwise indicated, the Panel recommends considering a trial of awake prone positioning to improve oxygenation (**CIIa**).
- The Panel **recommends against** using awake prone positioning as a rescue therapy for refractory hypoxemia to avoid intubation in patients who otherwise meet the indications for intubation and mechanical ventilation (**AIII**).
- If intubation becomes necessary, the procedure should be performed by an experienced practitioner in a controlled setting due to the enhanced risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exposure to health care practitioners during intubation (**AIII**).

Rationale

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

Goal of Oxygenation

The optimal oxygen saturation (SpO_2) in adults with COVID-19 is uncertain. However, a target SpO_2 of 92% to 96% seems logical considering that indirect evidence from experience in patients without COVID-19 suggests that an $\text{SpO}_2 < 92\%$ or $> 96\%$ may be harmful.

Regarding the potential harm of maintaining an $\text{SpO}_2 < 92\%$, a trial randomly assigned ARDS patients without COVID-19 to either a conservative oxygen strategy (target SpO_2 of 88% to 92%) or a liberal oxygen strategy (target $\text{SpO}_2 \geq 96\%$). The trial was stopped early due to futility after enrolling 205 patients, but in the conservative oxygen group there was increased mortality at 90 days (between-group risk difference of 14%; 95% CI, 0.7% to 27%) and a trend toward increased mortality at 28-days (between-group risk difference of 8%; 95% CI, -5% to 21%).¹

Regarding the potential harm of maintaining an $\text{SpO}_2 > 96\%$, a meta-analysis of 25 randomized trials involving patients without COVID-19 found that a liberal oxygen strategy (median SpO_2 of 96%) was associated with an increased risk of in-hospital mortality compared to a lower SpO_2 comparator (relative

risk 1.21; 95% CI, 1.03–1.43).²

Acute Hypoxemic Respiratory Failure

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

High-Flow Nasal Cannula and Noninvasive Positive Pressure Ventilation

HFNC is preferred over NIPPV in patients with acute hypoxemic respiratory failure based on data from an unblinded clinical trial in patients without COVID-19 who had acute hypoxemic respiratory failure. Study participants were randomized to HFNC, conventional oxygen therapy, or NIPPV. The patients in the HFNC group had more ventilator-free days (24 days) than those in the conventional oxygen therapy group (22 days) or NIPPV group (19 days) ($P = 0.02$), and 90-day mortality was lower in the HFNC group than in either the conventional oxygen therapy group (HR 2.01; 95% CI, 1.01–3.99) or the NIPPV group (HR 2.50; 95% CI, 1.31–4.78).³ In the subgroup of more severely hypoxemic patients ($\text{PaO}_2/\text{FiO}_2$ mm Hg ≤ 200), the intubation rate was lower for HFNC than for conventional oxygen therapy or NIPPV (HR 2.07 and 2.57, respectively).

The trial's findings were corroborated by a meta-analysis of eight trials with 1,084 patients conducted to assess the effectiveness of oxygenation strategies prior to intubation. Compared to NIPPV, HFNC reduced the rate of intubation (OR 0.48; 95% CI, 0.31–0.73) and ICU mortality (OR 0.36; 95% CI, 0.20–0.63).⁴

NIPPV may generate aerosol spread of SARS-CoV-2 and thus increase nosocomial transmission of the infection.^{5,6} It remains unclear whether HFNC results in a lower risk of nosocomial SARS-CoV-2 transmission than NIPPV.

Prone Positioning for Nonintubated Patients

Although prone positioning has been shown to improve oxygenation and outcomes in patients with moderate-to-severe ARDS who are receiving mechanical ventilation,^{7,8} there is less evidence regarding the benefit of prone positioning in awake patients who require supplemental oxygen without mechanical ventilation. In a case series of 50 patients with COVID-19 pneumonia who required supplemental oxygen upon presentation to a New York City emergency department, awake prone positioning improved the overall median oxygen saturation of the patients. However, 13 patients still required intubation due to respiratory failure within 24 hours of presentation to the emergency department.⁹ Other case series of patients with COVID-19 requiring oxygen or NIPPV have similarly reported that awake prone positioning is well-tolerated and improves oxygenation,¹⁰⁻¹² with some series also reporting low intubation rates after proning.^{10,12}

A prospective feasibility study of awake prone positioning in 56 patients with COVID-19 receiving HFNC or NIPPV in a single Italian hospital found that prone positioning for ≤ 3 hours was feasible in 84% of the patients. There was a significant improvement in oxygenation during prone positioning ($\text{PaO}_2/\text{FiO}_2$ 181 mm Hg in supine position vs. $\text{PaO}_2/\text{FiO}_2$ 286 mm Hg in prone position). However, when compared with baseline oxygenation before initiation of prone positioning, this improvement in oxygenation was not sustained ($\text{PaO}_2/\text{FiO}_2$ of 181 mm Hg and 192 mm Hg at baseline and 1 hour after resupination, respectively). Among patients put in the prone position, there was no difference in intubation rate between patients who maintained improved oxygenation (i.e., responders) and nonresponders.⁹

A prospective, multicenter observational cohort study in Spain and Andorra evaluated the effect of prone positioning on the rate of intubation in COVID-19 patients with acute respiratory failure receiving

HFNC. Of the 199 patients requiring HFNC, 55 (27.6%) were treated with prone positioning. Although the time to intubation was 1 day (IQR 1.0–2.5) in patients receiving HFNC and prone positioning versus 2 days [IQR 1.0–3.0] in patients receiving only HFNC ($P = 0.055$), the use of awake prone positioning did not reduce the risk of intubation (RR 0.87; 95% CI, 0.53–1.43; $P = 0.60$).¹³

Overall, despite promising data, it is unclear which hypoxemic, nonintubated patients with COVID-19 pneumonia benefit from prone positioning, how long prone positioning should be continued, or whether the technique prevents the need for intubation or improves survival.¹⁰

Appropriate candidates for awake prone positioning are those who can adjust their position independently and tolerate lying prone. Awake prone positioning is **contraindicated** in patients who are in respiratory distress and who require immediate intubation. Awake prone positioning is also **contraindicated** in patients who are hemodynamically unstable, patients who recently had abdominal surgery, and patients who have an unstable spine.¹⁴ Awake prone positioning is acceptable and feasible for pregnant patients and can be performed in the left lateral decubitus position or the fully prone position.¹⁵

Intubation for Invasive Mechanical Ventilation

It is essential to monitor hypoxemic patients with COVID-19 closely for signs of respiratory decompensation. To ensure the safety of both patients and health care workers, intubation should be performed in a controlled setting by an experienced practitioner.

Mechanically Ventilated Adults

Recommendations

For mechanically ventilated adults with COVID-19 and ARDS:

- The Panel recommends using low tidal volume (VT) ventilation (VT 4–8 mL/kg of predicted body weight) over higher VT ventilation (VT >8 mL/kg) (**AI**).
- The Panel recommends targeting plateau pressures of <30 cm H₂O (**AIIa**).
- The Panel recommends using a conservative fluid strategy over a liberal fluid strategy (**BIIa**).
- The Panel **recommends against** the routine use of inhaled nitric oxide (**AIIa**).

Rationale

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

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

Recommendations

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

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

Rationale

PEEP is beneficial in patients with ARDS because it prevents alveolar collapse, improves oxygenation, and minimizes atelectotrauma, a source of ventilator-induced lung injury. A meta-analysis of individual patient data from the three largest trials that compared lower and higher levels of PEEP in patients without COVID-19 found lower rates of ICU mortality and in-hospital mortality with higher PEEP in those with moderate ($\text{PaO}_2/\text{FiO}_2$ 100–200 mm Hg) and severe ARDS ($\text{PaO}_2/\text{FiO}_2 < 100$ mm Hg).¹⁶

Although there is no clear standard as to what constitutes a high level of PEEP, one conventional threshold is >10 cm H_2O .¹⁷ Recent reports have suggested that, in contrast to patients with non-COVID-19 causes of ARDS, some patients with moderate or severe ARDS due to COVID-19 have normal static lung compliance and thus, in these patients, higher PEEP levels may cause harm by compromising hemodynamics and cardiovascular performance.^{18,19} Other studies reported that patients with moderate to severe ARDS due to COVID-19 had low compliance, similar to the lung compliance seen in patients with conventional ARDS.^{20–23} These seemingly contradictory observations suggest that COVID-19 patients with ARDS are a heterogeneous population and assessment for responsiveness to higher PEEP should be individualized based on oxygenation and lung compliance. Clinicians should monitor patients for known side effects of higher PEEP, such as barotrauma and hypotension.

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

Recommendations

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

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

Rationale

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

Rescue Therapies for Mechanically Ventilated Adults With Acute Respiratory Distress Syndrome

Recommendations

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

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

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

Rationale

There are no studies to date assessing the effect of recruitment maneuvers on oxygenation in severe ARDS due to COVID-19. However, a systematic review and meta-analysis of six trials of recruitment maneuvers in non-COVID-19 patients with ARDS found that recruitment maneuvers reduced mortality, improved oxygenation 24 hours after the maneuver, and decreased the need for rescue therapy.²⁴ Because recruitment maneuvers can cause barotrauma or hypotension, patients should be closely monitored during recruitment maneuvers. If a patient decompensates during recruitment maneuvers, the maneuver should be stopped immediately. The importance of properly performing recruitment maneuvers was illustrated by an analysis of eight randomized controlled trials in non-COVID-19 patients (n = 2,544) which found that recruitment maneuvers did not reduce hospital mortality (RR 0.90; 95% CI, 0.78–1.04). Subgroup analysis found that traditional recruitment maneuvers significantly reduced hospital mortality (RR 0.85; 95% CI, 0.75–0.97), whereas incremental PEEP titration recruitment maneuvers increased mortality (RR 1.06; 95% CI, 0.97–1.17).²⁵

Although there are no published studies of inhaled nitric oxide in patients with COVID-19, a Cochrane review of 13 trials of inhaled nitric oxide use in patients with ARDS found no mortality benefit.²⁶ Because the review showed a transient benefit in oxygenation, it is reasonable to attempt inhaled nitric oxide as a rescue therapy in COVID patients with severe ARDS after other options have failed. However, if there is no benefit in oxygenation with inhaled nitric oxide, it should be tapered quickly to avoid rebound pulmonary vasoconstriction that may occur with discontinuation after prolonged use.

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Acute Kidney Injury and Renal Replacement Therapy

Last Updated: December 17, 2020

Recommendations

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

Rationale

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

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

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

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Pharmacologic Interventions

Last Updated: October 9, 2020

Antiviral Therapy

See [Therapeutic Management of Patients with COVID-19](#) for recommendations on the use of remdesivir with or without corticosteroids.

Immune-Based Therapy

Several immune-based therapies that are expected to modify the course of COVID-19, including corticosteroids, are currently under investigation or are already in use. These agents may target the virus (e.g., convalescent plasma) or modulate the immune response (e.g., corticosteroids, interleukin [IL]-1 or IL-6 inhibitors). Recommendations regarding immune-based therapy can be found in [Immunomodulators Under Evaluation for the Treatment of COVID-19](#).

Corticosteroids

See [Therapeutic Management of Patients with COVID-19](#) for recommendations on the use of dexamethasone with or without remdesivir.

Adjunctive Therapy

Recommendations for using adjunctive therapy in a critical care setting can be found in the [Antithrombotic Therapy](#) and [Vitamin C](#) sections.

Empiric Broad-Spectrum Antimicrobial Therapy

Recommendations

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

Rationale

There are no reliable estimates of the incidence or prevalence of copathogens with severe acute respiratory syndrome coronavirus 2 at this time.

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

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

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

Extracorporeal Membrane Oxygenation

Last Updated: December 17, 2020

Recommendation

- There are insufficient data to recommend either for or against the use of extracorporeal membrane oxygenation (ECMO) in 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](#)

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Therapeutic Management of Patients With COVID-19

Last Updated: April 21, 2021

Executive Summary

Two main processes are thought to drive the pathogenesis of COVID-19. Early in the clinical course, the disease is primarily driven by 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 antiviral therapies 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.

No therapy has been proven to be beneficial in outpatients with mild to moderate COVID-19 who are not at high risk for disease progression. The COVID-19 Treatment Guidelines Panel (the Panel) recommends providing supportive care and symptomatic management to outpatients with COVID-19; steps should also be taken to reduce the risk of SARS-CoV-2 transmission to others.^{1,2} Patients should be advised about when to seek in-person evaluation. See [Outpatient Management of Acute COVID-19](#) for more information.

In outpatients with mild to moderate COVID-19 who are at high risk for disease progression, anti-SARS-CoV-2 antibody-based therapies may have the greatest potential for clinical benefit during the earliest stages of infection. For these patients, the Panel recommends administering **bamlanivimab plus etesevimab (AIIa)** or **casirivimab plus imdevimab (AIIa)**, both of which are available through Emergency Use Authorizations (EUAs) from the Food and Drug Administration (FDA). See [Anti-SARS-CoV-2 Monoclonal Antibodies](#) for more information about using these combinations and other monoclonal antibodies.

Remdesivir, an antiviral agent, is currently the only drug that is approved by the FDA for the treatment of COVID-19. It is recommended for use in hospitalized patients who require supplemental oxygen. However, it is not routinely recommended for patients who require mechanical ventilation due to the lack of data showing benefit at this advanced stage of the disease.³⁻⁶

Dexamethasone, a corticosteroid, has been found to improve survival in hospitalized patients who require supplemental oxygen, with the greatest benefit observed in patients who require mechanical ventilation. Therefore, the use of dexamethasone is strongly recommended in this setting.⁷⁻¹⁰

Adding tocilizumab, a recombinant humanized anti-interleukin-6 receptor monoclonal antibody, to dexamethasone therapy was found to improve survival among patients who were exhibiting rapid respiratory decompensation due to COVID-19.^{11,12}

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

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

Doses and durations are listed in the footnotes.

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS
Not Hospitalized, Mild to Moderate COVID-19	<p>For patients who are not at high risk for disease progression, provide supportive care and symptomatic management (AIII).</p> <p>For patients who are at high risk of disease progression (as defined by the FDA EUA criteria for treatment with anti-SARS-CoV-2 monoclonal antibodies), use one of the following combinations:</p> <ul style="list-style-type: none"> • Bamlanivimab plus etesevimab (AIIa) • Casirivimab plus imdevimab (AIIa)
Hospitalized but Does Not Require Supplemental Oxygen	<p>There are insufficient data to recommend either for or against the routine use of remdesivir. For patients at high risk of disease progression, the use of remdesivir may be appropriate.</p>
Hospitalized and Requires Supplemental Oxygen	<p>Use one of the following options:</p> <ul style="list-style-type: none"> • Remdesivir^{a,b} (e.g., for patients who require minimal supplemental oxygen) (BIIa) • Dexamethasone^c plus remdesivir^{a,b} (e.g., for patients who require increasing amounts of supplemental oxygen) (BIII)^{d,e} • Dexamethasone^c (e.g., when combination therapy with remdesivir cannot be used or is not available) (BI)
Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	<p>Use one of the following options:</p> <ul style="list-style-type: none"> • Dexamethasone^c (AI)^e • Dexamethasone^c plus remdesivir^{a,b} (BIII)^{d,e} <p>For patients who were recently hospitalized^f with rapidly increasing oxygen needs and systemic inflammation:</p> <ul style="list-style-type: none"> • Add tocilizumab^g to one of the two options above (BIIa)
Hospitalized and Requires Invasive Mechanical Ventilation or ECMO	<ul style="list-style-type: none"> • Dexamethasone^c (AI)^h <p>For patients who are within 24 hours of admission to the ICU:</p> <ul style="list-style-type: none"> • Dexamethasone^c plus tocilizumab^g (BIIa)
<p>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</p>	

^a The remdesivir dose is 200 mg IV for one dose, followed by remdesivir 100 mg IV once daily for 4 days or until hospital discharge (unless the patient is in a health care setting that can provide acute care that is similar to inpatient hospital care). Treatment duration may be extended to up to 10 days if there is no substantial clinical improvement by Day 5.

^b For patients who are receiving remdesivir but progress to requiring oxygen through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or ECMO, remdesivir should be continued until the treatment course is completed.

^c The dexamethasone dose is 6 mg IV or PO once daily for 10 days or until hospital discharge. If dexamethasone is not available, equivalent doses of other corticosteroids (e.g., prednisone, methylprednisolone, hydrocortisone) may be used. See the Corticosteroids section for more information.

^d The combination of dexamethasone and remdesivir has not been studied in clinical trials.

^e In the rare circumstances where corticosteroids cannot be used, **baricitinib plus remdesivir** can be used (**BIIa**). The FDA has issued an EUA for baricitinib use in combination with remdesivir. The dose for baricitinib is 4 mg PO once daily for 14 days or until hospital discharge.

^f For example, within 3 days of hospital admission. See the Interleukin-6 Inhibitors section for more information.

^g The tocilizumab dose is 8 mg/kg of actual body weight (up to 800 mg) administered as a single IV dose. Tocilizumab should not be combined with baricitinib and should be avoided in certain groups of patients who are at increased risk for complications. See the Interleukin-6 Inhibitors section for more information.

^h 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.

Key: ECMO = extracorporeal membrane oxygenation; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; ICU = intensive care unit; IV = intravenous; the Panel = the COVID-19 Treatment Guidelines Panel; PO = orally

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

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

Recommendations

For patients who are not at high risk of disease progression:

- The Panel recommends providing supportive care and symptomatic management (**AIII**).

For patients who are at high risk of disease progression, as defined by the EUA criteria for treatment with anti-SARS-CoV-2 monoclonal antibodies:

- The Panel recommends using one of the following combination anti-SARS-CoV-2 monoclonal antibodies (treatments are listed in alphabetical order):
 - **Bamlanivimab 700 mg plus etesevimab 1,400 mg (AIIa); or**
 - **Casirivimab 1,200 mg plus imdevimab 1,200 mg (AIIa).**
- Treatment should be started as soon as possible after the patient receives a positive result on a SARS-CoV-2 antigen test or a nucleic acid amplification test and within 10 days of symptom onset.

Additional Considerations

- There are no comparative data to determine whether there are differences in clinical efficacy or safety between bamlanivimab plus etesevimab and casirivimab plus imdevimab.
 - There are SARS-CoV-2 variants, particularly those that contain the mutation E484K, that reduce the virus' susceptibility to bamlanivimab and, to a lesser extent, casirivimab and etesevimab in vitro; however, the clinical impact of these mutations is not known.
 - In regions where SARS-CoV-2 variants with reduced in vitro susceptibility to bamlanivimab plus etesevimab are common, some Panel members would preferentially use casirivimab plus imdevimab while acknowledging that it is not known whether in vitro susceptibility data correlate with clinical outcomes.

Rationale for Recommending Supportive Care and Symptomatic Management for Patients Who Are Not at High Risk of Disease Progression

No specific therapy has been proven to be beneficial in outpatients with mild to moderate COVID-19 who are not at high risk for disease progression. The Panel recommends supportive care and symptomatic management (**AIII**), with close monitoring for worsening symptoms and clinical deterioration for patients.

Rationale for the Use of Combination Anti-SARS-CoV-2 Monoclonal Antibodies

Two anti-SARS-CoV-2 combination products—bamlanivimab plus etesevimab and casirivimab plus imdevimab—have received EUAs from the FDA for the treatment of outpatients with mild to moderate COVID-19 who are at high risk of disease progression (as defined by the EUA). The FDA had previously issued an EUA for bamlanivimab alone. Due to the increase in circulating variants that have the potential for resistance to bamlanivimab, that EUA has since been revoked.

Several circulating SARS-CoV-2 variants, particularly those that contain the mutation E484K, are associated with reduced susceptibility to bamlanivimab and, to a lesser extent, casirivimab and etesevimab in vitro. However, the clinical impact of these mutations is not known. Reduced in vitro susceptibility to both antibodies in a combination regimen is currently uncommon. Please see [Anti-](#)

[SARS-CoV-2 Monoclonal Antibodies](#) for more information regarding the circulating SARS-CoV-2 variants of concern and interest and the susceptibility of these variants to anti-SARS-CoV-2 monoclonal antibodies.

The clinical trial data that demonstrate the clinical benefit of these anti-SARS-CoV-2 monoclonal antibody combinations for the treatment of outpatients with mild to moderate COVID-19 are outlined below. It is worth noting that these studies were conducted before the widespread circulation of the variants of concern.

Clinical Data

Bamlanivimab Plus Etesevimab

The EUA for bamlanivimab plus etesevimab was based on data from several studies, including the [Blocking Viral Attachment and Cell Entry With SARS-CoV-2 Neutralizing Antibodies](#) (BLAZE)-1 and [BLAZE-4](#) trials.

In the Phase 3 BLAZE-1 trial, a randomized trial that included 1,035 high-risk participants, the primary endpoint was the proportion of participants who had a COVID-19-related hospitalization (defined as ≥ 24 hours of acute care) or who died from any cause by Day 29. Compared to those who received placebo, participants who received bamlanivimab 2,800 mg plus etesevimab 2,800 mg had a 5% absolute reduction and a 70% relative reduction in COVID-19-related hospitalizations or death from any cause; endpoint events occurred in 11 of 518 participants (2.1%) in the bamlanivimab plus etesevimab arm and in 36 of 517 participants (7.0%) in the placebo arm ($P = 0.0004$). There were no deaths in the bamlanivimab plus etesevimab arm, and 10 deaths occurred in the placebo arm.^{13,14}

Of note, the doses authorized in the EUA (bamlanivimab 700 mg plus etesevimab 1,400 mg) are different from the doses studied in the Phase 3 BLAZE-1 study. The available data suggest that the antiviral activity of this lower dose is similar to that of bamlanivimab 2,800 mg plus etesevimab 2,800 mg.¹⁴

Casirivimab Plus Imdevimab

The recommendation for the use of casirivimab plus imdevimab is based on Phase 3 results from the [R10933-10987-COV-2067](#) study (the information from this study is currently available only in a press release, and there is no peer-reviewed preprint or publication).¹⁵ This trial compared 1,355 participants who received casirivimab 1,200 mg plus imdevimab 1,200 mg to 1,341 participants who received placebo.

The modified full analysis set included participants who were aged ≥ 18 years and had a positive SARS-CoV-2 polymerase chain reaction result from a nasopharyngeal swab at randomization and one or more risk factors for severe COVID-19. COVID-19-related hospitalizations or death from any cause were reported in 18 of 1,355 participants (1.3%) in the casirivimab plus imdevimab arm and in 62 of 1,341 participants (4.6%) in the placebo arm ($P < 0.0001$). This represents a 3.3% absolute reduction and a 71% relative reduction in hospitalization or death in the casirivimab plus imdevimab treatment participants.

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

Recommendations

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

Rationale for Recommending Against the Use of Dexamethasone or Other Corticosteroids

In the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial, a multicenter, open-label trial in the United Kingdom, hospitalized patients with COVID-19 were randomized to receive either dexamethasone plus standard of care or standard of care alone (control arm).⁷ In the subgroup of participants who did not require supplemental oxygen at enrollment, no survival benefit was observed for dexamethasone: 17.8% of participants in the dexamethasone arm and 14% in the control arm died within 28 days of enrollment (rate ratio 1.19; 95% CI, 0.91–1.55). Please see [Table 4a](#) for additional information. Based on these data, the Panel **recommends against** the use of **dexamethasone (AIIa)** or **other corticosteroids (AIII)** for the treatment of COVID-19 in this subgroup, unless the patient has another indication for corticosteroid therapy.

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

The Adaptive COVID-19 Treatment Trial (ACTT-1) was a multinational randomized controlled trial that compared remdesivir to placebo in hospitalized patients with COVID-19. Remdesivir showed no significant benefit in patients with mild to moderate disease, which was defined as oxygen saturation >94% on room air or a respiratory rate <24 breaths/min without supplemental oxygen (rate ratio for recovery 1.29; 95% CI, 0.91–1.83); however, there were only 138 patients in this group.³

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

The Solidarity trial was a large, multinational, open-label randomized controlled trial in which a 10-day course of remdesivir was compared to standard of care. About 25% of hospitalized patients in the remdesivir and control arms did not require supplemental oxygen at study entry. The primary outcome of in-hospital mortality occurred in 11 of 661 patients (2%) in the remdesivir arm and in 13 of 664 patients (2.1%) in the control arm (rate ratio 0.90; 99% CI, 0.31–2.58).¹⁶ The open-label design of this study makes it difficult to determine whether remdesivir affects recovery time as determined by duration of hospitalization, because patient discharge may have been delayed in order to complete remdesivir therapy. Please see [Table 2a](#) for additional information.

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

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

Recommendations

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

- **Remdesivir** (e.g., for patients who require minimal supplemental oxygen) (**BIIa**);
- **Dexamethasone plus remdesivir** (e.g., for patients who require increasing amounts of oxygen) (**BIII**); *or*

- **Dexamethasone** (e.g., when combination therapy with remdesivir cannot be used or is not available) (**BI**).

Additional Considerations

- If dexamethasone is not available, an alternative corticosteroid such as **prednisone**, **methylprednisolone**, or **hydrocortisone** can be used (**BIII**). See [Corticosteroids](#) for dosing recommendations.
- In the rare circumstances when corticosteroids cannot be used, **baricitinib plus remdesivir** can be used (**BIIa**). Baricitinib **should not be used** without remdesivir.
- There is insufficient evidence to determine which patients in this group would benefit from adding tocilizumab to dexamethasone treatment. Some Panel members would add tocilizumab to a patient's dexamethasone treatment in cases where the patient has rapidly increasing oxygen needs and C-reactive protein (CRP) levels ≥ 75 mg/L but does not yet require oxygen through high-flow nasal canula (HFNC) or noninvasive ventilation.

Rationale for the Use of Remdesivir

In ACTT-1, remdesivir was associated with improved time to recovery in the subgroup of participants (n = 435) who required oxygen supplementation but not high-flow oxygen, noninvasive ventilation, or mechanical ventilation (7 days for remdesivir vs. 9 days for placebo; recovery rate ratio 1.45; 95% CI, 1.18–1.79). A lower percentage of patients in the remdesivir arm than in the placebo arm progressed to requiring high-flow oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) among those who were not using these methods of oxygen delivery at baseline (17% vs. 24%). In a post hoc analysis of deaths by Day 29, remdesivir appeared to confer a substantial survival benefit in this subgroup (HR for death 0.30; 95% CI, 0.14–0.64).³

The Solidarity trial reported no difference in the rate of in-hospital deaths between patients who received remdesivir and those who received standard of care (rate ratio for death in the overall study population 0.95; 95% CI, 0.81–1.11; rate ratio for death in patients who did not require mechanical ventilation at entry 0.86; 99% CI, 0.67–1.11). There was no difference between patients who received remdesivir and those who received standard of care in the percentage of patients who progressed to invasive mechanical ventilation (11.9% vs. 11.5%) or in length of hospital stay.¹⁶ However, an open-label trial like Solidarity is less well-suited to assess time to recovery than a placebo-controlled trial. In Solidarity, because both clinicians and patients knew that remdesivir was being administered, it is possible that the hospital discharge could have been delayed in order to complete the 10-day course of therapy.

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

Rationale for the Use of Remdesivir Plus Dexamethasone

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

that is a consequence of the infection.

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

Rationale for the Use of Dexamethasone

In the RECOVERY trial, treatment with dexamethasone conferred a survival benefit among participants who required supplemental oxygen at enrollment. In the dexamethasone group, 23.3% of participants died within 28 days of enrollment compared with 26.2% in the standard of care arm (rate ratio 0.82; 95% CI, 0.72–0.94).⁷ However, the amount of supplemental oxygen that participants were receiving and the proportions of participants who required oxygen delivery through a high-flow device or noninvasive ventilation were not reported. It is possible that the benefit of dexamethasone was greatest in those who required more respiratory support. It should be noted that <0.1% of patients in the RECOVERY trial received concomitant remdesivir. For more information, please see the [Corticosteroids](#) section.

However, some experts prefer not to use dexamethasone monotherapy in this group because of the theoretical concern that corticosteroids might slow viral clearance when they are administered without an antiviral drug. Corticosteroids have been associated with delayed viral clearance and/or worse clinical outcomes in patients with other viral respiratory infections.¹⁷⁻¹⁹ Some studies have suggested that corticosteroids slow SARS-CoV-2 clearance, but the results to date are inconclusive.²⁰⁻²⁴

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

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

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

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

Rationale for the Panel's Assessment That There Are Insufficient Data to Determine Which Patients Would Benefit From Dexamethasone Plus Tocilizumab

Early trials that evaluated the use of tocilizumab in patients who were hospitalized with COVID-19 did

not show a treatment effect for tocilizumab. These trials included a high proportion of patients who were receiving conventional oxygen therapy; however, many of these trials were underpowered, and only a small proportion of patients were also receiving corticosteroids.²⁵⁻²⁹ Although the RECOVERY trial reported a mortality benefit for tocilizumab, the study did not identify a particular subgroup of hospitalized patients on conventional oxygen therapy who benefited most from receiving the drug.¹² Among 21,550 participants who were randomized into the RECOVERY platform trial, only 4,116 of the participants (19%) underwent a second randomization into the tocilizumab intervention arm, suggesting that the study results are generalizable only to a restricted subset of hospitalized patients. The Consolidated Standards of Reporting Trials (CONSORT) flow diagram for the RECOVERY trial suggests that patients with clinical evidence of progressive COVID-19 were preferentially selected for the tocilizumab study.

The Panel recognizes that there may be some hospitalized patients who are receiving conventional oxygen therapy who may have progressive hypoxemia associated with significant systemic inflammation. The addition of tocilizumab to their standard treatment may provide a modest benefit. Nevertheless, there is insufficient evidence to clearly characterize the subgroups within this patient population who would benefit from receiving tocilizumab.

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

Recommendations

- The Panel recommends one of the following options for these patients:
 - **Dexamethasone** alone (**AI**); *or*
 - A combination of **dexamethasone plus remdesivir** (**BIII**).
- For patients who were recently hospitalized and who have rapidly increasing oxygen needs and systemic inflammation, add **tocilizumab** to one of the two options above (**BIIa**).

Additional Considerations

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

- Although some patients in the Randomised, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) and RECOVERY trials received a second dose of tocilizumab at the discretion of their treating physicians, there are insufficient data 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. Prophylactic treatment with ivermectin should be considered for patients who are from areas where strongyloidiasis is endemic.

Rationale for the Use of Dexamethasone

In the RECOVERY study, treatment with dexamethasone conferred a survival benefit among participants who required supplemental oxygen without invasive mechanical ventilation at enrollment: 23.3% of the participants in the dexamethasone group died within 28 days of enrollment compared with 26.2% in the standard of care arm (rate ratio 0.82; 95% CI, 0.72–0.94).⁷

Rationale for the Use of Remdesivir Plus Dexamethasone

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

Rationale for Not Recommending Remdesivir Monotherapy

In ACTT-1, there was no observed difference in time to recovery between the remdesivir and placebo groups (recovery rate ratio 1.09; 95% CI, 0.76–1.57) in the subgroup of participants who required high-flow oxygen or noninvasive ventilation at enrollment (n = 193). A post hoc analysis did not show a survival benefit for remdesivir at Day 29.³ However, the trial was not powered to detect differences in outcomes within subgroups. The Panel **does not recommend** using **remdesivir monotherapy** in these patients because there is uncertainty regarding whether remdesivir alone confers a clinical benefit in this subgroup (**AIIa**). Dexamethasone or remdesivir plus dexamethasone are better treatment options for COVID-19 in this group of patients.

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

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

The REMAP-CAP and RECOVERY studies, the two largest randomized controlled tocilizumab trials to date, have both reported a mortality benefit for tocilizumab among patients with rapid respiratory decompensation who require oxygen delivery through HFNC or noninvasive ventilation.^{11,12} Corticosteroids were given to a majority of patients in both studies. In REMAP-CAP, a narrowly defined population of patients who were admitted to an intensive care unit (ICU) with severe to critical COVID-19 and who were exhibiting rapid respiratory decompensation were randomized to receive open-label tocilizumab or usual care alone. Compared to usual care, the use of tocilizumab reduced in-hospital mortality (28% vs. 36%) and increased the number of days free of respiratory and

cardiovascular organ support (10 days vs. 0 days; OR 1.64; 95% CI, 1.25–2.14). Enrollment occurred within 24 hours of ICU admission and within a median of 1.2 days of hospitalization (IQR 0.8–2.8 days), suggesting that the benefit of tocilizumab occurs specifically in patients who are experiencing rapid respiratory decompensation. In REMAP-CAP, the evidence for therapeutic benefit was strongest among recipients who had recently started oxygen supplementation through HFNC or noninvasive ventilation, though the lack of subgroup analyses by oxygen requirement is a notable limitation of this study.

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

The Panel **recommends against** using **tocilizumab** without concomitant corticosteroids, as multiple trials have reported that the clinical benefit of tocilizumab is seen among patients who are receiving tocilizumab plus a corticosteroid (see [Table 4b](#)).

Rationale for Using Baricitinib Plus Remdesivir When Corticosteroids Are Contraindicated

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

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

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

Recommendations

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

Additional Considerations

- If dexamethasone is not available, equivalent doses of alternative corticosteroids such as **prednisone, methylprednisolone, or hydrocortisone** may be used (**BIII**).

- For patients who initially received remdesivir monotherapy and progressed to requiring invasive mechanical ventilation or ECMO, dexamethasone should be initiated and remdesivir should be continued until the treatment course is completed.
- The Panel **recommends against** the use of **remdesivir monotherapy (AIIa)**.
- Tocilizumab should be given only in combination with dexamethasone (or another corticosteroid at an equivalent dose).
- Although some patients in the REMAP-CAP and RECOVERY trials received a second dose of tocilizumab at the discretion of their treating physicians, there are insufficient data 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. Prophylactic treatment with ivermectin should be considered for patients who are from areas where strongyloidiasis is endemic.

Rationale for the Use of Dexamethasone Monotherapy

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

Dexamethasone reduces mortality in critically ill patients with COVID-19 according to a meta-analysis that aggregated seven randomized trials and included data on 1,703 critically ill patients.³⁰ The largest trial in the meta-analysis was the RECOVERY trial, whose subgroup of mechanically ventilated patients was included.⁷ For details about the meta-analysis and the RECOVERY trial, see the [Corticosteroids](#) section. Because the benefits outweigh the potential harms, the Panel recommends the use of **dexamethasone** in hospitalized patients with COVID-19 who require invasive mechanical ventilation or ECMO (**AI**).

Considerations Related to the Use of Dexamethasone Plus Remdesivir Combination Therapy

Dexamethasone plus remdesivir combination therapy has not been evaluated in controlled studies; therefore, there is insufficient information to make a recommendation either for or against the use of this combination therapy. There is, however, a theoretical reason to administer dexamethasone plus remdesivir 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.^{17,18}

Some studies have suggested that corticosteroids slow SARS-CoV-2 clearance, but the studies to date are not definitive. For example, an observational study in people with non-severe COVID-19 suggested that viral clearance was delayed in patients who received corticosteroids,³¹ 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.²⁴ Given the conflicting results from observational studies and the absence of clinical trial data, some Panel members would coadminister **dexamethasone and remdesivir** in patients who have recently been placed on mechanical ventilation (**CIII**) until more conclusive evidence becomes available, based on their concerns about delayed viral clearance in patients who received corticosteroids. Other Panel members would not coadminister these drugs due to uncertainties about the benefit of using remdesivir in critically ill patients.

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

The REMAP-CAP and RECOVERY studies, the two largest randomized controlled tocilizumab trials to date, have both reported a mortality benefit for tocilizumab among patients who were recently admitted

to the ICU with rapid respiratory decompensation, including those who required invasive mechanical ventilation.^{11,12} REMAP-CAP enrolled patients within 24 hours of admission to the ICU. Prior trials that enrolled patients later in the ICU course and/or who received oxygen support >24 hours after ICU admission have failed to show consistent clinical benefits from tocilizumab (see [Table 4b](#)). Thus, it is unclear whether there is a clinical benefit for tocilizumab in patients who received invasive mechanical ventilation more than 24 hours after ICU admission. Findings from RECOVERY suggest a clinical benefit for tocilizumab among patients with rapid clinical progression who received invasive mechanical ventilation, tocilizumab, and corticosteroids. See the section above for additional details on the clinical trial data and rationale for using tocilizumab in this situation.

Rationale for Recommending Against the Use of Remdesivir Monotherapy

A clear benefit of remdesivir monotherapy has not been demonstrated in patients who require invasive mechanical ventilation or ECMO. During ACTT-1, remdesivir did not improve the recovery rate in this subgroup of participants (recovery rate ratio 0.98; 95% CI, 0.70–1.36), and in a post hoc analysis of deaths by Day 29, remdesivir did not improve survival among participants in this subgroup (HR 1.13; 95% CI, 0.67–1.89).³ In the Solidarity trial, there was a trend toward increased mortality among patients who received mechanical ventilation and who were randomized to receive remdesivir rather than standard of care (rate ratio 1.27; 95% CI, 0.99–1.62).¹⁶ Taken together, these results do not demonstrate a clear benefit of remdesivir in critically ill patients.

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

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

Last Updated: February 11, 2021

Summary Recommendations
<p>Remdesivir is the only Food and Drug Administration-approved drug for the treatment of COVID-19. In this section, the COVID-19 Treatment Guidelines Panel (the Panel) provides recommendations for using antiviral drugs to treat COVID-19 based on the available data. As in the management of any disease, treatment decisions ultimately reside with the patient and their health care provider. For more information on these antiviral agents, see Table 2d.</p>
<p>Remdesivir</p> <ul style="list-style-type: none">• See Therapeutic Management of Patients with COVID-19 for recommendations on using remdesivir with or without dexamethasone.
<p>Chloroquine or Hydroxychloroquine With or Without Azithromycin</p> <ul style="list-style-type: none">• The Panel recommends against the use of chloroquine or hydroxychloroquine with or without azithromycin for the treatment of COVID-19 in hospitalized patients (AI).• In nonhospitalized patients, the Panel recommends against the use of chloroquine or hydroxychloroquine with or without azithromycin for the treatment of COVID-19, except in a clinical trial (AIIa).• The Panel recommends against the use of high-dose chloroquine (600 mg twice daily for 10 days) for the treatment of COVID-19 (AI).
<p>Lopinavir/Ritonavir and Other HIV Protease Inhibitors</p> <ul style="list-style-type: none">• 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).
<p>Ivermectin</p> <ul style="list-style-type: none">• There are insufficient data for the Panel to recommend either for or against the use of ivermectin for the treatment of COVID-19. Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of ivermectin in the treatment of COVID-19.
<p>Rating of Recommendations: A = Strong; B = Moderate; C = Optional</p> <p>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</p>

Antiviral Therapy

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

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

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Remdesivir

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Remdesivir is an intravenous nucleotide prodrug of an adenosine analog. Remdesivir binds to the viral RNA-dependent RNA polymerase and inhibits viral replication through premature termination of RNA transcription. It has demonstrated in vitro activity against SARS-CoV-2.¹ In a rhesus macaque model of SARS-CoV-2 infection, remdesivir treatment was initiated soon after inoculation; the remdesivir-treated animals had lower virus levels in the lungs and less lung damage than the control animals.²

Remdesivir is approved by the Food and Drug Administration (FDA) for the treatment of COVID-19 in hospitalized adult and pediatric patients (aged ≥ 12 years and weighing ≥ 40 kg). It is also available through an FDA Emergency Use Authorization (EUA) for the treatment of COVID-19 in hospitalized pediatric patients weighing 3.5 kg to < 40 kg or aged < 12 years and weighing ≥ 3.5 kg. Remdesivir should be administered in a hospital or a health care setting that can provide a similar level of care to an inpatient hospital.

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

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

Monitoring and Adverse Effects

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

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

Considerations in Patients With Renal Insufficiency

Each 100 mg vial of remdesivir lyophilized powder contains 3 g of sulfobutylether beta-cyclodextrin sodium (SBECD), whereas each 100 mg/20 mL vial of remdesivir solution contains 6 g of SBECD.³ SBECD is a vehicle that is primarily eliminated through the kidneys. A patient with COVID-19 who receives a loading dose of remdesivir 200 mg would receive 6 g to 12 g of SBECD, depending on the formulation. This amount of SBECD is within the safety threshold for patients with normal renal function.⁴ Accumulation of SBECD in patients with renal impairment may result in liver and renal toxicities. Clinicians may consider preferentially using the lyophilized powder formulation (which contains less SBECD) in patients with renal impairment.

Because both remdesivir formulations contain SBECD, patients with an estimated glomerular filtration rate (eGFR) of < 50 mL/min were excluded from some clinical trials of remdesivir; other trials had an eGFR cutoff of < 30 mL/min. Remdesivir **is not recommended** for patients with an eGFR < 30 mL/min

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

In two observational studies that evaluated the use of remdesivir in hospitalized patients with COVID-19, no significant differences were reported in the incidences of adverse effects or acute kidney injury between patients with an estimated creatinine clearance (CrCl) <30 mL/min and those with an estimated CrCl ≥30 mL/min.^{6,7} One of these studies evaluated patients who primarily received the solution formulation of remdesivir (20 patients had an estimated CrCl <30 mL/min and 115 had an estimated CrCl ≥30 mL/min);⁶ the other study evaluated patients who received the lyophilized powder formulation (40 patients had an estimated CrCl <30 mL/min and 307 had an estimated CrCl ≥30 mL/min).⁷

Drug-Drug Interactions

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

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

See [Table 2d](#) for more information.

Considerations in Pregnancy

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

Considerations in Children

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

Clinical Trials

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

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Table 2a. Remdesivir: Selected Clinical Data

Last Updated: February 11, 2021

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

Study Design	Methods	Results	Limitations and Interpretation
Adaptive COVID-19 Treatment Trial (ACTT-1)¹			
<p>Multinational, placebo-controlled, double-blind RCT in hospitalized patients (n = 1,062)</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged ≥18 years • Laboratory-confirmed SARS-CoV-2 infection • At least 1 of the following conditions: <ul style="list-style-type: none"> • Pulmonary infiltrates, as determined by radiographic imaging • SpO₂ ≤94% on room air • Required supplemental oxygen • Required mechanical ventilation • Required ECMO <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • ALT or AST >5 times ULN • eGFR <30 mL/min • Pregnancy or breastfeeding <p>Interventions:</p> <ul style="list-style-type: none"> • IV RDV 200 mg on Day 1, then 100 mg daily for up to 9 more days • Placebo for 10 days <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Time to clinical recovery <p>Ordinal Scale Definitions:</p> <ol style="list-style-type: none"> 1. Not hospitalized, no limitations 2. Not hospitalized, with limitations 3. Hospitalized, no active medical problems 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • RDV (n = 541) and placebo (n = 521) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Median time from symptom onset to randomization was 9 days (IQR 6–12 days). <p>Outcomes</p> <p><i>Overall Results:</i></p> <ul style="list-style-type: none"> • RDV reduced time to recovery compared to placebo (10 days vs. 15 days; RRR 1.29; 95% CI, 1.12–1.49; <i>P</i> < 0.001). • Clinical improvement based on ordinal scale was higher at Day 15 in RDV arm (OR 1.5; 95% CI, 1.2–1.9; <i>P</i> < 0.001). • No statistically significant difference in mortality by Day 29 between RDV and placebo arms (HR 0.73; 95% CI, 0.52–1.03; <i>P</i> = 0.07). • Benefit of RDV was greatest in patients randomized during the first 10 days after symptom onset. <p><i>Results by Disease Severity at Enrollment:</i></p> <ul style="list-style-type: none"> • No difference in median time to recovery between arms among patients who had mild to moderate disease at enrollment. • Benefit of RDV for reducing time to recovery was clearest in patients who required supplemental oxygenation at enrollment (n = 435; RRR 1.45; 95% CI, 1.18–1.79), and RDV appeared to confer 	<p>Limitations:</p> <ul style="list-style-type: none"> • Wide range of disease severity; study was not powered to detect differences within subgroups • Powered to detect differences in clinical improvement, not mortality • No data collected on longer-term morbidity <p>Interpretation:</p> <ul style="list-style-type: none"> • In patients with severe COVID-19, RDV reduced time to clinical recovery. • Benefit of RDV was most apparent in hospitalized patients on supplemental oxygen. • No observed benefit in those on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO, but the study was not powered to detect differences within subgroups. • No observed benefit of RDV in patients with mild or moderate COVID-19, but the number of participants in these categories was relatively small.

Study Design	Methods	Results	Limitations and Interpretation
Adaptive COVID-19 Treatment Trial (ACTT-1)¹, continued			
	4. Hospitalized, not on oxygen 5. Hospitalized, on oxygen 6. Hospitalized, on high-flow oxygen or noninvasive mechanical ventilation 7. Hospitalized, on mechanical ventilation or ECMO 8. Death	a survival benefit in this subgroup (HR for death by Day 29 0.30; 95% CI, 0.14–0.64). <ul style="list-style-type: none"> • No observed difference in time to recovery between arms in patients on high-flow oxygen or noninvasive ventilation at enrollment (RRR 1.09; 95% CI, 0.76–1.57). No evidence that RDV affected mortality rate in this subgroup (HR 1.02; 95% CI, 0.54–1.91). • No observed difference in time to recovery between arms in patients on mechanical ventilation or ECMO at enrollment (RRR 0.98; 95% CI, 0.70–1.36). No evidence that RDV affected mortality rate in this subgroup (HR 1.13; 95% CI, 0.67–1.89). <i>Safety Results:</i> <ul style="list-style-type: none"> • Percentages of patients with SAEs were similar between arms (25% vs. 32%). • Transaminase elevations: 6% of RDV recipients, 10.7% of placebo recipients 	
Remdesivir Versus Placebo for Severe COVID-19 in China²			
Multicenter, placebo-controlled, double-blind RCT in hospitalized patients with severe COVID-19 (n = 237)	Key Inclusion Criteria: <ul style="list-style-type: none"> • Aged ≥18 years • Laboratory-confirmed SARS-CoV-2 infection • Time from symptom onset to randomization <12 days • SpO₂ ≤94% on room air or PaO₂/FiO₂ <300 mm Hg • Radiographically confirmed pneumonia Key Exclusion Criteria: <ul style="list-style-type: none"> • ALT or AST >5 times ULN • eGFR <30 mL/min • Pregnancy or breastfeeding 	Number of Participants: <ul style="list-style-type: none"> • ITT analysis: RDV (n = 158) and placebo (n = 78) • Study stopped before reaching target enrollment of 453 patients due to control of the COVID-19 outbreak in China. Participant Characteristics: <ul style="list-style-type: none"> • Median time from symptom onset to randomization: 9 days for RDV arm, 10 days for placebo arm • Receipt of corticosteroids: 65% of patients in RDV arm, 68% in placebo arm • Receipt of LPV/RTV: 28% of patients in RDV arm, 29% in placebo arm 	Limitations: <ul style="list-style-type: none"> • Sample size did not have sufficient power to detect differences in clinical outcomes. • Use of concomitant medications (i.e., corticosteroids, LPV/RTV, IFNs) may have obscured effects of RDV. Interpretation: <ul style="list-style-type: none"> • No difference in time to clinical improvement, 28-day mortality, or rate of SARS-CoV-2 clearance between RDV-treated and placebo-treated patients;

Study Design	Methods	Results	Limitations and Interpretation
Remdesivir Versus Placebo for Severe COVID-19 in China², continued			
	<p>Interventions:</p> <ul style="list-style-type: none"> • IV RDV 200 mg on Day 1, then 100 mg daily for 9 days • Saline placebo for 10 days <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Time to clinical improvement, defined as improvement on an ordinal scale or being discharged alive from the hospital 	<ul style="list-style-type: none"> • Receipt of IFN alfa-2b: 29% of patients in RDV arm, 38% in placebo arm <p>Outcomes:</p> <ul style="list-style-type: none"> • No difference in time to clinical improvement between RDV and placebo arms (median time 21 days vs. 23 days; HR 1.23; 95% CI, 0.87–1.75). • For patients who started RDV or placebo within 10 days of symptom onset, faster time to clinical improvement was seen with RDV (median time 18 days vs. 23 days; HR 1.52; 95% CI, 0.95–2.43); however, this was not statistically significant. • 28-day mortality was similar between arms (14% of patients in RDV arm, 13% in placebo arm). • No difference between arms in SARS-CoV-2 viral load at baseline, and rate of decline over time was similar. • Percentage of patients with AEs: 66% in RDV arm, 64% in placebo arm • Discontinuations due to AEs: 12% of patients in RDV arm, 5% in placebo arm 	<p>however, study was underpowered to detect differences in these outcomes between arms.</p>
World Health Organization Solidarity Trial³			
<p>International, open-label, adaptive RCT with multiple treatment arms that enrolled hospitalized patients with COVID-19 (n = 11,330). In 1 arm, patients received RDV.</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged ≥ 18 years • Not known to have received any study drug • Not expected to be transferred elsewhere within 72 hours • Physician reported no contraindications to study drugs <p>Interventions:</p> <ul style="list-style-type: none"> • IV RDV 200 mg on Day 0, then 100 mg daily on Days 1–9 • Local SOC 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • ITT analysis: RDV (n = 2,743) and SOC (n = 2,708) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Percentage of patients aged 50–69 years: 47% in RDV arm, 48% in SOC arm • Percentage of patients aged ≥ 70 years: 18% in RDV arm, 17% in SOC arm • 67% of patients in both arms were on supplemental oxygen at entry. • 9% of patients in both arms were mechanically ventilated at entry. 	<p>Limitations:</p> <ul style="list-style-type: none"> • Open-label study design limits the ability to assess time to recovery; clinicians and patients were aware of treatment assignment, so RDV may have been continued to complete the treatment course even if the patient had improved. • No data on time from symptom onset to enrollment • No assessment of outcomes post hospital discharge

Study Design	Methods	Results	Limitations and Interpretation
World Health Organization Solidarity Trial³, continued			
	<p>Primary Endpoint:</p> <ul style="list-style-type: none"> In-hospital mortality <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> Initiation of mechanical ventilation Duration of hospitalization 	<ul style="list-style-type: none"> Percentage of patients hospitalized for ≥ 2 days at entry: 40% in RDV arm, 39% in SOC arm Percentages of patients with comorbid conditions were similar between RDV and SOC arms: diabetes (26% and 25%), heart disease (21% both groups), and chronic lung disease (6% and 5%). 48% of patients in both arms received corticosteroids. <p>Primary Outcomes:</p> <ul style="list-style-type: none"> In-hospital mortality: 301 deaths (11.0%) in RDV arm, 303 deaths (11.2%) in SOC arm Rate ratios for in-hospital death: <ul style="list-style-type: none"> Overall: 0.95 (95% CI, 0.81–1.11) No mechanical ventilation at entry: 0.86 (99% CI, 0.67–1.11) Mechanical ventilation at entry: 1.20 (99% CI, 0.80–1.80) <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> Initiation of mechanical ventilation: 295 patients (10.8%) in RDV arm, 284 patients (10.5%) in SOC arm 	<p>Interpretation:</p> <ul style="list-style-type: none"> RDV did not decrease in-hospital mortality in hospitalized patients when compared to local SOC.
Remdesivir Versus Standard of Care in Hospitalized Patients with Moderate COVID-19⁴			
Open-label randomized trial in hospitalized patients (n = 596)	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> Laboratory-confirmed SARS-CoV-2 infection Moderate pneumonia, defined as radiographic evidence of pulmonary infiltrates and SpO₂ >94% on room air <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> ALT or AST >5 times ULN CrCl <50 mL/min 	<p>Number of Participants:</p> <ul style="list-style-type: none"> 584 patients began treatment: 10-day RDV (n = 193), 5-day RDV (n = 191), and SOC (n = 200) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> Demographic and baseline disease characteristics were similar across all arms. <p>Outcomes:</p> <ul style="list-style-type: none"> 5-day RDV had significantly higher odds of better clinical status distribution on Day 11 than SOC (OR 1.65; 95% CI, 1.09–2.48; <i>P</i> = 0.02). 	<p>Limitations:</p> <ul style="list-style-type: none"> Open-label design may have affected decisions related to concomitant medication use and hospital discharge. Greater proportion of patients in SOC arm received HCQ, LPV/RTV, or AZM, which may cause AEs and have not shown clinical benefits in hospitalized patients with COVID-19.

Study Design	Methods	Results	Limitations and Interpretation
Remdesivir Versus Standard of Care in Hospitalized Patients with Moderate COVID-19⁴ , continued			
	<p>Interventions:</p> <ul style="list-style-type: none"> • IV RDV 200 mg on Day 1, then 100 mg daily for 9 days • IV RDV 200 mg on Day 1, then 100 mg daily for 4 days • Local SOC <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Clinical status on Day 11, as measured by a 7-point ordinal scale 	<ul style="list-style-type: none"> • Clinical status distribution on Day 11 was not significantly different between the 10-day RDV and SOC arms ($P = 0.18$). • By Day 28, there were more hospital discharges among patients who received RDV (89% in 5-day arm and 90% in 10-day arm) than those who received SOC (83%). • Mortality was low in all arms (1% to 2%). • Percentages of patients with AEs in RDV arms vs. SOC arm: nausea (10% vs. 3%), hypokalemia (6% vs. 2%), and headache (5% vs. 3%) 	<ul style="list-style-type: none"> • No data on time to return to activity for discharged patients <p>Interpretation:</p> <ul style="list-style-type: none"> • Hospitalized patients with moderate COVID-19 who received 5 days of RDV had better outcomes than those who received SOC; however, difference between arms was of uncertain clinical importance.
Different Durations of Remdesivir Treatment in Hospitalized Patients⁵			
<p>Manufacturer-sponsored, multinational, randomized, open-label trial in hospitalized patients with COVID-19 (n = 402)</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged ≥ 12 years • Laboratory-confirmed SARS-CoV-2 infection • Radiographic evidence of pulmonary infiltrates • SpO₂ $\leq 94\%$ on room air or receipt of supplemental oxygen <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Receipt of mechanical ventilation or ECMO • Multiorgan failure • ALT or AST > 5 times ULN • Estimated CrCl < 50 mL/min <p>Interventions:</p> <ul style="list-style-type: none"> • IV RDV 200 mg on Day 1, then 100 mg daily for 4 days • IV RDV 200 mg on Day 1, then 100 mg daily for 9 days <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Clinical status at Day 14, as measured by a 7-point ordinal scale 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • 397 participants began treatment: 5-day RDV (n = 200) and 10-day RDV (n = 197) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • At baseline, patients in 10-day arm had worse clinical status (based on ordinal scale distribution) than those in 5-day arm ($P = 0.02$) <p>Outcomes:</p> <ul style="list-style-type: none"> • After adjusting for imbalances in baseline clinical status, Day 14 distribution in clinical status on the ordinal scale was similar between arms ($P = 0.14$). • Time to achieve clinical improvement of at least 2 levels on the ordinal scale (median day of 50% cumulative incidence) was similar between arms (10 days vs. 11 days). • Median durations of hospitalization among patients discharged on or before Day 14 were similar between 5-day (7 days; IQR 6–10 days) and 10-day arms (8 days; IQR 5–10 days). • Percentages of patients with SAEs: 35% in 10-day arm, 21% in 5-day arm 	<p>Limitations:</p> <ul style="list-style-type: none"> • This was an open-label trial without a placebo control arm, so clinical benefit of RDV (compared with no RDV) could not be assessed. • There were baseline imbalances in clinical status of patients in the 5-day and 10-day arms. <p>Interpretation:</p> <ul style="list-style-type: none"> • In hospitalized patients with severe COVID-19 who were not on mechanical ventilation or ECMO, RDV treatment for 5 or 10 days had a similar clinical benefit.

Study Design	Methods	Results	Limitations and Interpretation
Different Durations of Remdesivir Treatment in Hospitalized Patients⁵ , continued			
		• Discontinuations due to AEs: 4% of patients in 5-day arm, 10% in 10-day arm	

Key: AE = adverse effects; ALT = alanine transaminase; AST = aspartate aminotransferase; AZM = azithromycin; CrCl = creatinine clearance; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; HCQ = hydroxychloroquine; IFN = interferon; ITT = intention to treat; IV = intravenous; LPV/RTV = lopinavir/ritonavir; the Panel = the COVID-19 Treatment Guidelines Panel; PaO₂/FiO₂ = ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; RCT = randomized controlled trial; RDV = remdesivir; RRR = recovery rate ratio; SAE = serious adverse effects; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOC = standard of care; SpO₂ = saturation of oxygen; ULN = upper limit of normal

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Chloroquine or Hydroxychloroquine With or Without Azithromycin

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Chloroquine is an antimalarial drug that was developed in 1934. Hydroxychloroquine, an analogue of chloroquine, was developed in 1946. Hydroxychloroquine is used to treat autoimmune diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis, in addition to malaria. In general, hydroxychloroquine has fewer and less severe toxicities (including less propensity to prolong the QTc interval) and fewer drug-drug interactions than chloroquine.

Both chloroquine and hydroxychloroquine increase the endosomal pH, inhibiting fusion of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the host cell membranes.¹ Chloroquine inhibits glycosylation of the cellular angiotensin-converting enzyme 2 receptor, which may interfere with binding of severe acute respiratory syndrome-associated coronavirus (SARS-CoV) to the cell receptor.² In vitro studies have suggested that both chloroquine and hydroxychloroquine may block the transport of SARS-CoV-2 from early endosomes to endolysosomes, possibly preventing the release of the viral genome.³ Both chloroquine and hydroxychloroquine also have immunomodulatory effects. It has been hypothesized that these effects are other potential mechanisms of action for the treatment of COVID-19. However, despite demonstrating antiviral activity in some in vitro systems, hydroxychloroquine with or without azithromycin did not reduce upper or lower respiratory tract viral loads or demonstrate clinical efficacy in a rhesus macaque model.⁴

Chloroquine and hydroxychloroquine, with or without azithromycin, have been studied in multiple clinical trials for the treatment of COVID-19. The recommendations below are based on an assessment of the collective evidence from these studies.

Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of **chloroquine** or **hydroxychloroquine** with or without **azithromycin** for the treatment of COVID-19 in hospitalized patients (**AI**).
- In nonhospitalized patients, the Panel **recommends against** the use of **chloroquine** or **hydroxychloroquine** with or without **azithromycin** for the treatment of COVID-19, except in a clinical trial (**AIIa**).
- The Panel **recommends against** the use of **high-dose chloroquine** (600 mg twice daily for 10 days) for the treatment of COVID-19 (**AI**).

Rationale

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

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

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

In addition to these randomized trials, data from large retrospective observational studies do not consistently show evidence of a benefit for hydroxychloroquine with or without azithromycin in hospitalized patients with COVID-19. For example, in a large retrospective observational study of patients who were hospitalized with COVID-19, hydroxychloroquine use was not associated with a reduced risk of death or mechanical ventilation.⁸ Another multicenter retrospective observational study evaluated the use of hydroxychloroquine with and without azithromycin in a random sample of a large cohort of hospitalized patients with COVID-19.⁹ Patients who received hydroxychloroquine with or without azithromycin did not have a decreased risk of in-hospital mortality when compared to those who received neither hydroxychloroquine nor azithromycin.

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

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

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

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

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

Please see [Table 2b](#) for additional details.

Adverse Effects

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

Cardiac Adverse Effects

- QTc prolongation, Torsade de Pointes, ventricular arrhythmia, and cardiac deaths.¹⁶ If chloroquine or hydroxychloroquine is used, clinicians should monitor the patient for adverse events, especially prolonged QTc interval (**AIII**).
- The risk of QTc prolongation is greater for chloroquine than for hydroxychloroquine.
- Concomitant medications that pose a moderate to high risk for QTc prolongation (e.g., antiarrhythmics, antipsychotics, antifungals, macrolides [including azithromycin],¹⁶ fluoroquinolone antibiotics)¹⁷ should be used only if necessary. Consider using doxycycline rather than azithromycin as empiric therapy for atypical pneumonia.
- Multiple studies have demonstrated that concomitant use of hydroxychloroquine and azithromycin can prolong the QTc interval;¹⁸⁻²⁰ in an observational study, the use of hydroxychloroquine plus azithromycin was associated with increased odds of cardiac arrest.⁹ The use of this combination warrants careful monitoring.
- Baseline and follow-up electrocardiograms are recommended when there are potential drug interactions with concomitant medications (e.g., azithromycin) or underlying cardiac diseases.²¹
- The risk-benefit ratio should be assessed for patients with cardiac disease, a history of ventricular arrhythmia, bradycardia (<50 bpm), or uncorrected hypokalemia and/or hypomagnesemia.

Other Adverse Effects

- Hypoglycemia, rash, and nausea. Divided doses may reduce nausea.
- Retinopathy. Bone marrow suppression may occur with long-term use, but this is not likely with short-term use.

Drug-Drug Interactions

Chloroquine and hydroxychloroquine are moderate inhibitors of cytochrome P450 (CYP) 2D6, and these drugs are also P-glycoprotein (P-gp) inhibitors. Use caution when administering these drugs with medications that are metabolized by CYP2D6 (e.g., certain antipsychotics, beta-blockers, selective serotonin reuptake inhibitors, methadone) or transported by P-gp (e.g., certain direct-acting oral anticoagulants, digoxin).²² Chloroquine and hydroxychloroquine may decrease the antiviral activity of remdesivir; coadministration of these drugs **is not recommended**.²³

Considerations in Pregnancy

- Antirheumatic doses of chloroquine and hydroxychloroquine have been used safely in pregnant women with SLE.

- Hydroxychloroquine exposure has not been associated with adverse pregnancy outcomes in ≥ 300 human pregnancies.
- A lower dose of chloroquine (500 mg once a week) is used for malaria prophylaxis during pregnancy.
- No dose changes are necessary for chloroquine or hydroxychloroquine during pregnancy.

Considerations in Children

- Chloroquine and hydroxychloroquine have been routinely used in pediatric populations for the treatment and prevention of malaria and for rheumatologic conditions.

Drug Availability

- Hydroxychloroquine, chloroquine, and azithromycin **are not approved** by the Food and Drug Administration (FDA) for the treatment of COVID-19.
- Hydroxychloroquine is approved by the FDA for the treatment of malaria, lupus erythematosus, and rheumatoid arthritis. Chloroquine is approved for the treatment of malaria and extraintestinal amebiasis. Azithromycin is commonly used for the treatment and/or prevention of nontuberculous mycobacterial infection, various sexually transmitted infections, and various bacterial infections.

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Table 2b. Chloroquine or Hydroxychloroquine With or Without Azithromycin: Selected Clinical Data

Last Updated: October 9, 2020

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](https://www.clinicaltrials.gov) for more information on clinical trials that are evaluating CQ, HCQ, and AZM.

The Panel has reviewed other clinical studies of HCQ with or without AZM and studies of CQ for the treatment of COVID-19.¹⁻¹¹ These studies have limitations that make them less definitive and informative than the studies discussed here. The Panel's summaries and interpretations of some of those studies are available in the [archived versions](#) of the COVID-19 Treatment Guidelines.

Study Design	Methods	Results	Limitations and Interpretation
Randomised Evaluation of COVID-19 Therapy (RECOVERY) Trial¹²			
<p>Open-label RCT with multiple arms, including a control arm; in 1 arm, hospitalized patients received HCQ (n = 11,197)</p> <p><i>This is a preliminary report that has not yet been peer reviewed.</i></p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> Clinically suspected or laboratory-confirmed SARS-CoV-2 infection <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> Patients with prolonged QTc intervals were excluded from HCQ arm. <p>Interventions:</p> <ul style="list-style-type: none"> HCQ 800 mg at entry and at 6 hours, then HCQ 400 mg every 12 hours for 9 days or until discharge Usual SOC <p>Primary Endpoint:</p> <ul style="list-style-type: none"> All-cause mortality at Day 28 after randomization 	<p>Number of Participants:</p> <ul style="list-style-type: none"> 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. <p>Participant Characteristics:</p> <ul style="list-style-type: none"> Mean age was 65 years in both arms; 41% of patients were aged ≥ 70 years. 90% of patients had laboratory-confirmed SARS-CoV-2 infection. 57% of patients had ≥ 1 major comorbidity: 27% had diabetes mellitus, 26% had heart disease, and 22% had chronic lung disease. At randomization, 17% of patients were receiving invasive mechanical ventilation or ECMO, 60% were receiving oxygen only (with or without noninvasive ventilation), and 24% were receiving neither. Use of AZM or another macrolide during the follow-up period was similar in both arms, as was use of dexamethasone. 	<p>Limitations:</p> <ul style="list-style-type: none"> Not blinded Information on occurrence of new major cardiac arrhythmia was not collected throughout the trial. <p>Interpretation:</p> <ul style="list-style-type: none"> HCQ does not decrease 28-day all-cause mortality when compared to the usual SOC in hospitalized patients with clinically suspected or laboratory-confirmed SARS-CoV-2 infection. Patients who received HCQ had a longer median length of hospital stay, and those who were not on invasive mechanical ventilation at the time of randomization were more likely to require intubation or die during hospitalization if they received HCQ.

Study Design	Methods	Results	Limitations and Interpretation
Randomised Evaluation of COVID-19 Therapy (RECOVERY) Trial¹², continued			
		<p>Outcomes:</p> <ul style="list-style-type: none"> • No significant difference in 28-day mortality between the 2 arms; 418 patients (26.8%) in HCQ arm and 788 patients (25.0%) in SOC arm had died by Day 28 (RR 1.09; 95% CI, 0.96–1.23; <i>P</i> = 0.18). • A similar 28-day mortality for HCQ patients was reported during the post hoc exploratory analysis that was restricted to the 4,234 participants (90%) who had a positive SARS-CoV-2 test result. • Patients in HCQ arm were less likely to survive hospitalization and had a longer median time to discharge than patients in SOC arm. • Patients who received HCQ and who were not on invasive mechanical ventilation at baseline had an increased risk of requiring intubation and an increased risk of death. • At the beginning of the study, the researchers did not record whether a patient developed a major cardiac arrhythmia after study enrollment; however, these data were later collected for 698 patients (44.7%) in HCQ arm and 1,357 patients (43.0%) in SOC arm. • No differences between the arms in the frequency of supraventricular tachycardia, ventricular tachycardia or fibrillation, or instances of AV block that required intervention. 	
Hydroxychloroquine and Hydroxychloroquine Plus Azithromycin for Mild or Moderate COVID-19¹³			
Open-label, 3-arm RCT in hospitalized patients (n = 667)	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged ≥18 years • Clinically suspected or laboratory-confirmed SARS-CoV-2 infection • Mild or moderate COVID-19 • Duration of symptoms ≤14 days 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • Modified ITT analysis included patients with laboratory-confirmed SARS-CoV-2 infection (n = 504). <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Mean age was 50 years. • 58% of patients were men. • At baseline, 58.2% of patients were ordinal level 3; 41.8% were ordinal level 4. • Median time from symptom onset to randomization was 7 days. 	<p>Limitations:</p> <ul style="list-style-type: none"> • Not blinded • Follow-up period was restricted to 15 days. <p>Interpretation:</p> <ul style="list-style-type: none"> • Neither HCQ alone nor HCQ plus AZM improved clinical outcomes at Day 15 after randomization among hospitalized patients with mild or moderate COVID-19.

Study Design	Methods	Results	Limitations and Interpretation
Hydroxychloroquine and Hydroxychloroquine Plus Azithromycin for Mild or Moderate COVID-19¹³, continued			
	<p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Need for >4 L of supplemental oxygen or $\geq 40\%$ FiO₂ by face mask • History of ventricular tachycardia • QT interval ≥ 480 ms <p>Interventions:</p> <ul style="list-style-type: none"> • 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 <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Clinical status at Day 15, as assessed by a 7-point ordinal scale among the patients with confirmed SARS-CoV-2 infection <p>Ordinal Scale Definitions:</p> <ol style="list-style-type: none"> 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 	<ul style="list-style-type: none"> • 23.3% to 23.9% of patients received oseltamivir. <p>Outcomes:</p> <ul style="list-style-type: none"> • No significant difference between the odds of worse clinical status at Day 15 for patients in HCQ arm (OR 1.21; 95% CI, 0.69–2.11; $P = 1.00$) and patients in HCQ plus AZM arm (OR 0.99; 95% CI, 0.57–1.73; $P = 1.00$). • No significant differences in secondary outcomes of the 3 arms, including progression to mechanical ventilation during the first 15 days and mean number of days “alive and free of respiratory support.” • A greater proportion of patients in HCQ plus AZM arm (39.3%) and HCQ arm (33.7%) experienced AEs than those in SOC arm (22.6%). • QT prolongation was more common in patients who received HCQ plus AZM or HCQ alone than in patients who received SOC alone, but fewer patients in SOC arm had serial electrocardiographic studies performed during the follow-up period. 	

Study Design	Methods	Results	Limitations and Interpretation
Hydroxychloroquine Versus Standard of Care for Mild or Moderate COVID-19¹⁴			
<p>Multicenter, randomized, open-label trial (n = 150)</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged ≥18 years • Laboratory-confirmed SARS-CoV-2 infection <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Severe conditions, including heart, liver, or kidney disease • Inability to take oral medications • Pregnancy or breastfeeding <p>Interventions:</p> <ul style="list-style-type: none"> • HCQ 1,200 mg once daily for 3 days, then HCQ 800 mg once daily for 2 weeks (in patients with mild or moderate COVID-19) or 3 weeks (in patients with severe disease) • SOC <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Negative conversion of SARS-CoV-2 by Day 28 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • HCQ (n = 75) and SOC (n = 75) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Patients were randomized at a mean of 16.6 days after symptom onset. • 99% of patients had mild or moderate COVID-19. <p>Outcomes:</p> <ul style="list-style-type: none"> • HCQ arm and SOC arm had similar negative PCR conversion rates within 28 days (85.4% of participants vs. 81.3% of participants) and similar times to negative PCR conversion (median of 8 days vs. 7 days). • No difference in the probability of symptom alleviation between the arms in the ITT analysis. 	<p>Limitations:</p> <ul style="list-style-type: none"> • Unclear how the overall rate of symptom alleviation was calculated • Study did not reach target sample size. <p>Interpretation:</p> <ul style="list-style-type: none"> • This study demonstrated no difference in the rate of viral clearance between HCQ and SOC.
High-Dose Chloroquine Versus Low-Dose Chloroquine¹⁵			
<p>Randomized, double-blind, Phase 2b study in hospitalized adults (n = 81)</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged ≥18 years • Clinically suspected COVID-19 • At least 1 of the following conditions: <ul style="list-style-type: none"> • Respiratory rate >24 rpm • Heart rate >125 bpm • SpO₂ <90% on room air • Shock 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • High-dose CQ (n = 41) and low-dose CQ (n = 40) • Planned study sample size was 440 participants, but study was stopped by the study's DSMB. <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • All patients also received ceftriaxone plus AZM. • 89.6% of patients received oseltamivir. 	<p>Limitations:</p> <ul style="list-style-type: none"> • More older patients and more patients with a history of heart disease were randomized into the high-dose arm than into the low-dose arm. <p>Interpretation:</p> <ul style="list-style-type: none"> • Despite the small number of patients enrolled, this study raises concerns about an increased risk of mortality when high-dose CQ is administered in combination with AZM and oseltamivir.

Study Design	Methods	Results	Limitations and Interpretation
High-Dose Chloroquine Versus Low-Dose Chloroquine¹⁵, continued			
	<p>Interventions:</p> <ul style="list-style-type: none"> • CQ 600 mg twice daily for 10 days (high dose) • CQ 450 mg twice daily for 1 day, then CQ 450 mg for 4 days (low dose) <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Mortality by Day 28 	<p>Outcomes:</p> <ul style="list-style-type: none"> • Overall fatality rate was 27.2%. • Mortality by Day 13 was higher in high-dose arm than in low-dose arm (death occurred in 16 of 41 patients [39%] vs. in 6 of 40 patients [15%]; $P = 0.03$). This difference was no longer significant after controlling for age (OR 2.8; 95% CI, 0.9–8.5). • Overall, QTcF >500 ms occurred more frequently in high-dose arm (18.9% of patients) than in low-dose arm (11.1%). • In the high-dose arm, 2 patients experienced ventricular tachycardia before death. 	
Hydroxychloroquine in Nonhospitalized Adults with Early COVID-19¹⁶			
<p>Randomized, placebo-controlled trial in the United States and Canada (n = 491)</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • ≤4 days of symptoms that were compatible with COVID-19 • Either laboratory-confirmed SARS-CoV-2 infection or high-risk exposure within the previous 14 days <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Aged <18 years • Hospitalized • Receipt of certain medications <p>Interventions:</p> <ul style="list-style-type: none"> • HCQ 800 mg once, then HCQ 600 mg in 6 to 8 hours, then HCQ 600 mg once daily for 4 days • Placebo 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • Contributed to primary endpoint data: HCQ (n = 212) and placebo (n = 211) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • 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. 	<p>Limitations:</p> <ul style="list-style-type: none"> • This study enrolled a highly heterogenous population. • Only 227 of 423 participants (53.7%) were confirmed PCR-positive for SARS-CoV-2. • Changing the primary endpoint without a new power calculation makes it difficult to assess whether the study is powered to detect differences in outcomes between the study arms. • This study used surveys for screening, symptom assessment, and adherence reporting. • Visual analog scales are not commonly used, and their ability to assess acute viral respiratory infections in clinical trials has not been validated.

Study Design	Methods	Results	Limitations and Interpretation
Hydroxychloroquine in Nonhospitalized Adults with Early COVID-19¹⁶, continued			
	<p>Primary Endpoints:</p> <ul style="list-style-type: none"> Planned primary endpoint was ordinal outcome by Day 14 in 4 categories: not hospitalized, hospitalized, ICU stay, or death. Because event rates were lower than expected, a new primary endpoint was defined: change in overall symptom severity over 14 days, assessed on a 10-point, self-reported, visual analog scale 	<p>Outcomes:</p> <ul style="list-style-type: none"> Compared to the placebo recipients, HCQ recipients had a nonsignificant 12% difference in improvement in symptoms between baseline and Day 14 (-2.60 vs. -2.33 points; $P = 0.117$). Ongoing symptoms were reported by 24% of those in HCQ arm and 30% of those in the placebo arm at Day 14 ($P = 0.21$). No difference in the incidence of hospitalization (4 patients in the HCQ arm vs. 10 patients in placebo arm); 2 of 10 placebo participants were hospitalized for reasons that were unrelated to COVID-19. A higher percentage of patients in HCQ arm experienced AEs than patients in placebo arm (43% vs. 22%; $P < 0.001$). 	<p>Interpretation:</p> <ul style="list-style-type: none"> The study has some limitations, and it did not find evidence that early administration of HCQ reduced symptom severity in patients with mild COVID-19.
Hydroxychloroquine in Nonhospitalized Adults with Mild COVID-19¹⁷			
Open-label RCT in Spain (n = 353)	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> Laboratory-confirmed SARS-CoV-2 infection <5 days of mild COVID-19 symptoms <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> Moderate to severe COVID-19 Severe liver or renal disease History of cardiac arrhythmia QT prolongation <p>Interventions:</p> <ul style="list-style-type: none"> HCQ 800 mg on Day 1, then HCQ 400 mg once daily for 6 days No antiviral treatment 	<p>Number of Participants:</p> <ul style="list-style-type: none"> 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. <p>Participant Characteristics:</p> <ul style="list-style-type: none"> 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. 	<p>Limitations:</p> <ul style="list-style-type: none"> Open-label, non-placebo-controlled trial Study design allowed for the possibility of drop-outs in control arm and over-reporting of AEs in HCQ arm. The intervention changed during the study; the authors initially planned to include HCQ plus DRV/COBI. The majority of the participants were relatively young health care workers. <p>Interpretation:</p> <ul style="list-style-type: none"> Early administration of HCQ to patients with mild COVID-19 did not result in improvement in virologic clearance, a lower risk of disease progression, or a reduced time to symptom improvement.

Study Design	Methods	Results	Limitations and Interpretation
Hydroxychloroquine in Nonhospitalized Adults with Mild COVID-19¹⁷, continued			
	<p>Primary Endpoint:</p> <ul style="list-style-type: none"> Reduction in SARS-CoV-2 viral load, assessed using nasopharyngeal swabs on Days 3 and 7 <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> Disease progression up to Day 28 Time to complete resolution of symptoms 	<p>Outcomes:</p> <ul style="list-style-type: none"> No significant difference in viral load reduction between control arm and HCQ arm at Day 3 (-1.41 vs. -1.41 log₁₀ copies/mL; difference of 0.01; 95% CI, -0.28 to 0.29), or at Day 7 (-3.37 vs. -3.44 log₁₀ copies/mL; difference of -0.07; 95% CI, -0.44 to 0.29). No difference in the risk of hospitalization between control arm and HCQ arm (7.1% vs. 5.9%; risk ratio 0.75; 95% CI, 0.32–1.77). No difference in the median time from randomization to the resolution of COVID-19 symptoms between the 2 arms (12.0 days in control arm vs. 10.0 days in HCQ arm; <i>P</i> = 0.38). A higher percentage of participants in the HCQ arm than in the control arm experienced AEs during the 28-day follow-up period (72% vs. 9%). Most common AEs were GI disorders and “nervous system disorders.” SAEs were reported in 12 patients in control arm and 8 patients in HCQ arm. SAEs that occurred among patients in HCQ arm were not deemed to be related to the drug. 	
Observational Study on Hydroxychloroquine With or Without Azithromycin¹⁸			
<p>Retrospective, multicenter, observational study in a random sample of inpatients with COVID-19 from the New York Department of Health (n = 1,438)</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> Laboratory-confirmed SARS-CoV-2 infection <p>Interventions:</p> <ul style="list-style-type: none"> HCQ plus AZM HCQ alone AZM alone Neither drug <p>Primary Endpoint:</p> <ul style="list-style-type: none"> In-hospital mortality 	<p>Number of Participants:</p> <ul style="list-style-type: none"> HCQ plus AZM (n = 735), HCQ alone (n = 271), AZM alone (n = 211), and neither drug (n = 221) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> Patients in the treatment arms had more severe disease at baseline than those who received neither drug. <p>Outcomes:</p> <ul style="list-style-type: none"> 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. 	<p>Limitations:</p> <ul style="list-style-type: none"> This study has the inherent limitations of an observational study, including residual confounding from confounding variables that were unrecognized and/or unavailable for analysis. <p>Interpretation:</p> <ul style="list-style-type: none"> Despite the limitations discussed above, these findings suggest that although HCQ and AZM are not associated with an increased risk of

Study Design	Methods	Results	Limitations and Interpretation
Observational Study on Hydroxychloroquine With or Without Azithromycin¹⁸, continued			
	Secondary Endpoint: <ul style="list-style-type: none"> Cardiac arrest and arrhythmia or QT prolongation on an ECG 	<ul style="list-style-type: none"> Patients who received HCQ plus AZM had a greater risk of cardiac arrest than patients who received neither drug (OR 2.13; 95% CI, 1.12–4.05). 	in-hospital death, the combination of HCQ and AZM may be associated with an increased risk of cardiac arrest.
Observational Study of Hydroxychloroquine Versus No Hydroxychloroquine in New York City¹⁹			
Observational study in hospitalized adults with COVID-19 at a large medical center (n = 1,376)	Key Inclusion Criteria: <ul style="list-style-type: none"> Laboratory-confirmed SARS-CoV-2 infection Key Exclusion Criteria: <ul style="list-style-type: none"> Intubation, death, or transfer to another facility within 24 hours of arriving at the emergency department Interventions: <ul style="list-style-type: none"> HCQ 600 mg twice daily on Day 1, then HCQ 400 mg once daily for 4 days No HCQ Primary Endpoint: <ul style="list-style-type: none"> Time from study baseline (24 hours after patients arrived at the emergency department) to intubation or death 	Number of Participants: <ul style="list-style-type: none"> Received HCQ (n = 811) and did not receive HCQ (n = 565) Participant Characteristics: <ul style="list-style-type: none"> HCQ recipients were more severely ill at baseline than those who did not receive HCQ. Outcomes: <ul style="list-style-type: none"> Using propensity scores to adjust for major predictors of respiratory failure and inverse probability weighting, the study demonstrated that HCQ use was not associated with intubation or death (HR 1.04; 95% CI, 0.82–1.32). No association between concomitant use of AZM and the composite endpoint of intubation or death (HR 1.03; 95% CI, 0.81–1.31). 	Limitations: <ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> The use of HCQ for treatment of COVID-19 was not associated with harm or benefit in a large observational study.
Observational Cohort Study of Hydroxychloroquine Versus No Hydroxychloroquine in France²⁰			
Retrospective, observational cohort study in hospitalized adults with severe COVID-19 pneumonia at 4 tertiary care centers (n = 181)	Key Inclusion Criteria: <ul style="list-style-type: none"> Aged 18 to 80 years Laboratory-confirmed SARS-CoV-2 infection Required supplemental oxygen Key Exclusion Criteria: <ul style="list-style-type: none"> Started HCQ before hospital admission 	Number of Participants: <ul style="list-style-type: none"> Received HCQ within 48 hours (n = 84), received HCQ beyond 48 hours (n = 8), and did not receive HCQ (n = 89) Participant Characteristics: <ul style="list-style-type: none"> In the HCQ arm, 18% of patients received concomitant AZM. 	Limitations: <ul style="list-style-type: none"> This was a retrospective, nonrandomized study. Interpretation: <ul style="list-style-type: none"> There was no difference in the rates of clinically important outcomes between patients who received HCQ within 48 hours of hospital admission and those who did not.

Study Design	Methods	Results	Limitations and Interpretation
Observational Cohort Study of Hydroxychloroquine Versus No Hydroxychloroquine in France²⁰ , continued			
	<ul style="list-style-type: none"> • Received tocilizumab, LPV/RTV, or RDV within 48 hours of admission • Organ failure requiring immediate ICU admission • ARDS <p>Interventions:</p> <ul style="list-style-type: none"> • HCQ 600 mg once daily • No HCQ <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Survival without transfer to the ICU at Day 21 <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> • Overall survival rate at Day 21 • Survival rate without ARDS at Day 21 • Weaning from oxygen by Day 21 • Discharge from hospital to home or rehabilitation by Day 21 	<p>Outcomes:</p> <ul style="list-style-type: none"> • In the inverse probability of treatment-weighted analysis, there was no difference in survival rates without ICU transfer at Day 21 between the HCQ arm (76% of participants) and the non-HCQ arm (75%). • No difference between the arms in the secondary outcomes of overall survival rate and survival rate without ARDS at Day 21. 	
Retrospective Cohort Study of Hydroxychloroquine Versus No Hydroxychloroquine in Detroit, Michigan²¹			
Comparative, retrospective cohort study in hospitalized patients with COVID-19 in the Henry Ford Health System in Michigan (n = 2,541)	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Laboratory-confirmed SARS-CoV-2 infection <p>Interventions:</p> <ul style="list-style-type: none"> • HCQ 400 mg twice daily for 1 day, then 200 mg twice daily for 4 days • AZM 500 mg for 1 day, then 250 mg once daily for 4 days • HCQ plus AZM, at the above doses • Neither drug 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • HCQ alone (n = 1,202), AZM alone (n = 147), HCQ plus AZM (n = 783), and neither drug (n = 409) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • HCQ plus AZM was reserved for patients with severe COVID-19 and minimal cardiac risks. • Median patient age was 64 years (IQR 53–76 years); 51% of patients were men, 56% were African American, and 52% had a BMI \geq30. • Median time to follow-up was 28.5 days (IQR 3–53 days). 	<p>Limitations:</p> <ul style="list-style-type: none"> • This study evaluated 1 health care system with an institutional protocol for HCQ and AZM use. • Because the study was not randomized and not blinded, there is a possibility of residual confounding. • There was a lower rate of ICU admission among patients who did not receive HCQ, which suggests that this group may have received less aggressive care.

Study Design	Methods	Results	Limitations and Interpretation
Retrospective Cohort Study of Hydroxychloroquine Versus No Hydroxychloroquine in Detroit, Michigan²¹, continued			
	<p>Primary Endpoint:</p> <ul style="list-style-type: none"> In-hospital mortality 	<ul style="list-style-type: none"> The mSOFA score was not available for 25% of patients. Corticosteroids were given to 79% of patients in the HCQ alone arm, 74% of patients in the HCQ plus AZM arm, and 35.7% of those on neither drug. <p>Outcomes:</p> <ul style="list-style-type: none"> Overall, crude mortality was 18.1%. When broken down by the different arms, mortality was 13.5% in HCQ alone arm, 20.1% in HCQ plus AZM arm, 22.4% in AZM alone arm, and 26.4% in the arm that received neither drug ($P < 0.001$). Mortality HRs were analyzed using a multivariable Cox regression model; the arm that received neither drug was used as the reference. HCQ alone decreased the mortality HR by 66% ($P < 0.001$). HCQ plus AZM decreased the mortality HR by 71% ($P < 0.001$). Other predictors of mortality were age ≥ 65 years (HR 2.6; 95% CI, 1.9–3.3); White race (HR 1.7; 95% CI, 1.4–2.1); chronic kidney disease (HR 1.7; 95% CI, 1.4–2.1); reduced O₂ saturation level on admission (HR 1.6; 95% CI, 1.1–2.2); and ventilator use at admission (HR 2.2; 95% CI, 1.4–3.0). A propensity-matched Cox regression result suggested a mortality HR of 0.487 for patients who received HCQ (95% CI, 0.285–0.832, $P = 0.009$). 	<ul style="list-style-type: none"> Given that the RECOVERY trial showed that dexamethasone use conferred a survival benefit, it is possible that the findings were confounded by the imbalance in corticosteroid use among the arms. <p>Interpretation:</p> <ul style="list-style-type: none"> This study reported a mortality benefit in hospitalized patients with COVID-19 who received either HCQ alone or HCQ plus AZM compared to patients who received neither drug. However, there were substantial imbalances in corticosteroid use among the arms, which may have affected mortality. Because the study was retrospective and observational, it cannot control for confounders.

Key: AE = adverse effect; ARDS = acute respiratory distress syndrome; AV = atrioventricular; AZM = azithromycin; BMI = body mass index; bpm = beats per minute; CQ = chloroquine; DRV/COBI = darunavir/cobicistat; DSMB = data safety monitoring board; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; FiO₂ = fraction of inspired oxygen; GI = gastrointestinal; HCQ = hydroxychloroquine; HFNC = high-flow nasal cannula; ICU = intensive care unit; ITT = intention to treat; LPV/RTV = lopinavir/ritonavir; mSOFA = modified sequential organ failure assessment; the Panel = the COVID-19 Treatment Guidelines Panel; PCR = polymerase chain reaction; QTcF = Fridericia's correction formula; RCT = randomized controlled trial; RDV = remdesivir; RR = rate ratio; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse effect; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOC = standard of care

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Ivermectin

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

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

Reports from in vitro studies suggest that ivermectin acts by inhibiting the host importin alpha/beta-1 nuclear transport proteins, which are part of a key intracellular transport process that viruses hijack to enhance infection by suppressing the host's antiviral response.^{4,5} In addition, ivermectin docking may interfere with the attachment of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein to the human cell membrane.⁶ Ivermectin is thought to be a host-directed agent, which may be the basis for its broad-spectrum activity in vitro against the viruses that cause dengue, Zika, HIV, and yellow fever.^{4,7-9} Despite this in vitro activity, no clinical trials have reported a clinical benefit for ivermectin in patients with these viruses. Some studies of ivermectin have also reported potential anti-inflammatory properties, which have been postulated to be beneficial in people with COVID-19.¹⁰⁻¹²

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

Recommendation

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

Rationale

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

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

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

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

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

Monitoring, Adverse Effects, and Drug-Drug Interactions

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

Considerations in Pregnancy

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

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

Considerations in Children

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

Clinical Trials

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

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Table 2c. Ivermectin: Selected Clinical Data

Last Updated: February 11, 2021

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

Study Design	Methods	Results	Limitations and Interpretation
Ivermectin Versus Ivermectin Plus Doxycycline Versus Placebo for Treatment of COVID-19¹			
Randomized, double-blind, placebo-controlled trial of hospitalized adults in Dhaka, Bangladesh (n = 72)	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged 18–65 years • Laboratory-confirmed SARS-CoV-2 infection with fever, cough, or sore throat • Admitted to hospital within previous 7 days <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Chronic cardiac, renal, or liver disease <p>Interventions:</p> <ul style="list-style-type: none"> • IVM 12 mg PO once daily for 5 days • Single dose of IVM 12 mg PO plus DOX 200 mg PO on Day 1, then DOX 100 mg every 12 hours for 4 days • Placebo <p>Primary Endpoints:</p> <ul style="list-style-type: none"> • Time to virologic clearance, measured by obtaining an NP swab for SARS-CoV-2 PCR on Days 3, 7, and 14, then weekly until PCR result was negative • Resolution of fever and cough within 7 days 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • IVM (n = 24; 2 withdrew), IVM plus DOX (n = 24; 1 withdrew), and placebo (n = 24; 1 withdrew) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Mean age was 42 years. • 54% of participants were female. • Mean time from symptom onset to assessment was 3.83 days. • No patients required supplemental oxygen. <p>Primary Outcomes:</p> <ul style="list-style-type: none"> • Shorter mean time to virologic clearance with IVM than placebo (9.7 days vs. 12.7 days; $P = 0.02$), but not with IVM plus DOX (11.5 days; $P = 0.27$). • Rates of virologic clearance were greater in IVM arm at Day 7 (HR 4.1; 95% CI, 1.1–14.7; $P = 0.03$) and at Day 14 (HR 2.7; 95% CI, 1.2–6.0; $P = 0.02$) compared to placebo, but not in the IVM plus DOX arm (HR 2.3; 95% CI, 0.6–9.0; $P = 0.22$ and HR 1.7; 95% CI, 0.8–4.0; $P = 0.19$). • No statistically significant difference in time to resolution of fever, cough, or sore throat between IVM and placebo arms ($P = 0.35$, $P = 0.18$, and $P = 0.35$, respectively) or IVM plus DOX and placebo arms ($P = 0.09$, $P = 0.23$, and $P = 0.09$, respectively). <p>Other Outcomes:</p> <ul style="list-style-type: none"> • Mean values of CRP, LDH, procalcitonin, and ferritin declined in all arms from baseline to Day 7, but there were no between-arm comparisons of the changes. • No between-arm differences in duration of hospitalization ($P = 0.93$). • No SAEs recorded. 	<p>Limitations:</p> <ul style="list-style-type: none"> • Small sample size • Not clear whether both IVM and DOX placebos were used. • Patients with chronic diseases were excluded. • Disease appears to have been mild in all participants; thus, the reason for hospitalization is unclear. • Absolute changes in inflammatory markers are not presented but were reportedly significant. • PCR results are not a validated surrogate marker for clinical efficacy. <p>Interpretation:</p> <ul style="list-style-type: none"> • A 5-day course of IVM resulted in faster virologic clearance than placebo, but not a faster time to resolution of symptoms (fever, cough, and sore throat). Because time to virologic clearance is not a validated surrogate marker for clinical efficacy, the clinical efficacy of IVM is unknown.

Study Design	Methods	Results	Limitations and Interpretation
Ivermectin Versus Placebo for Outpatients With Mild COVID-19²			
<p>Open-label RCT of adult outpatients in Lahore, Pakistan (n = 50)</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • SARS-CoV-2 PCR positive • Mild disease <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Severe symptoms likely related to cytokine storm • Malignancy, chronic kidney disease, or cirrhosis • Pregnancy <p>Interventions:</p> <ul style="list-style-type: none"> • IVM 12 mg PO immediately, followed by 12 mg doses at 12 and 24 hours, plus symptomatic treatment • Symptomatic treatment <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Symptoms reported on Day 7. Patients were stratified as asymptomatic or symptomatic. 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • IVM (n = 25) and control (n = 25) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Mean age was 40.6 years. • 62% of participants were male. • 40% of participants had diabetes, 30% were smokers, 26% had hypertension, 8% had cardiovascular disease, and 12% had obesity. <p>Outcomes:</p> <ul style="list-style-type: none"> • Proportion of asymptomatic patients at Day 7 was similar in IVM and control arms (64% vs. 60%; <i>P</i> = 0.500). • AEs were attributed to IVM in 8 patients (32%). 	<p>Limitations:</p> <ul style="list-style-type: none"> • Small sample size • Open-label study • Authors reported the proportions of participants with certain symptoms and comorbidities but did not provide objective assessment of disease severity. This precludes the ability to compare outcomes between arms. • Study classified outcomes at Day 7 as “symptomatic” and “asymptomatic,” but did not account for symptom worsening or improvement. <p>Interpretation:</p> <ul style="list-style-type: none"> • IVM showed no effect on symptom resolution in patients with mild COVID-19.
Ivermectin Plus Doxycycline Versus Hydroxychloroquine Plus Azithromycin for Asymptomatic Patients and Patients with Mild to Moderate COVID-19³			
<p>RCT of outpatients with SARS-CoV-2 infection with or without symptoms in Bangladesh (n = 116)</p> <p><i>This is a preliminary report that has not yet been peer reviewed.</i></p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Laboratory-confirmed SARS-CoV-2 infection by RT-PCR • SpO₂ ≥95% • Normal or near-normal CXR • No unstable comorbidities <p>Interventions</p> <p><i>Group A:</i></p> <ul style="list-style-type: none"> • A single dose of IVM 200 µg/kg plus DOX 100 mg twice daily for 10 days 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • Group A (n = 60) and Group B (n = 56) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Mean age was 33.9 years. • 72% of participants were male. • 91 of 116 participants (78.5%) were symptomatic. <p>Outcomes:</p> <ul style="list-style-type: none"> • In Group A, PCR became negative in 60 of 60 patients (100%). Mean time to negative PCR result was 8.93 days (range 8–13 days). 	<p>Limitations:</p> <ul style="list-style-type: none"> • Small sample size • Open-label study • No SOC alone group • Study enrolled young patients without major risk factors for disease progression. • None of the comparative outcome measures were statistically significant.

Study Design	Methods	Results	Limitations and Interpretation
Ivermectin Plus Doxycycline Versus Hydroxychloroquine Plus Azithromycin for Asymptomatic Patients and Patients with Mild to Moderate COVID-19³, continued			
	<p><i>Group B:</i></p> <ul style="list-style-type: none"> • HCQ 400 mg on Day 1, then HCQ 200 mg twice daily for 9 days plus AZM 500 mg once daily for 5 days <p>Primary Endpoints:</p> <ul style="list-style-type: none"> • Time to negative PCR result. Asymptomatic patients were tested starting on Day 5, then every other day until a negative result occurred. Symptomatic patients were tested on their second symptom-free day, then every other day until a negative result occurred. • Time to resolution of symptoms 	<ul style="list-style-type: none"> • In Group B, PCR became negative in 54 of 56 patients (96.4%). Mean time to negative PCR result was 9.33 days (range 5–15 days). • Difference between groups in time from recovery to negative PCR result was not statistically significant ($P = 0.2314$). • In a subgroup analysis of patients who were symptomatic at baseline, the mean durations to negative PCR for Groups A and B were 9.06 days and 9.74 days, respectively ($P = 0.0714$). • In the subgroup analysis, the mean symptom recovery durations for Groups A and B were 5.93 days (range 5–10 days) and 6.99 days (range 4–12 days), respectively ($P = 0.071$). • Patients receiving IVM plus DOX had fewer AEs than those receiving HCQ plus AZM (31.7% vs. 46.4%) in the subgroup analysis. 	<p>Interpretation:</p> <ul style="list-style-type: none"> • In this small study with a young population, the authors suggested that IVM plus DOX was superior to HCQ plus AZM despite no statistically significant difference in time from recovery to negative PCR result and symptom recovery between patients who received IVM plus DOX and those who received HCQ plus AZM.
Effect of Early Treatment With Ivermectin Versus Placebo on Viral Load, Symptoms, and Humoral Response in Patients With Mild COVID-19⁴			
<p>A single-center, randomized, double-blind, placebo-controlled pilot trial in Spain (n = 24)</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Laboratory-confirmed SARS-CoV-2 infection • ≤72 hours of symptoms • No risk factors for severe disease or COVID-19 pneumonia <p>Interventions:</p> <ul style="list-style-type: none"> • Single dose of IVM 400 µg/kg • Nonmatching placebo tablet administered by a nurse who did not participate in the patient's care <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Positive SARS-CoV-2 PCR result from an NP swab at Day 7 post-treatment 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • IVM (n = 12) and placebo (n = 12) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Mean age was 26 years (range 18–54 years). • 50% of participants were male. • All participants had symptoms at baseline; 70% had headache, 66% had fever, 58% had malaise, and 25% had cough. • Median onset of symptoms was 24 hours in IVM arm and 48 hours in placebo arm. <p>Outcomes:</p> <ul style="list-style-type: none"> • At Day 7, 12 patients (100%) in both groups had a positive PCR (for gene N), and 11 of 12 who received IVM (92%) and 12 of 12 who received placebo (100%) had a positive PCR (for gene E); $P = 1.0$ for both comparisons. • In a post hoc analysis, the authors reported fewer patient-days of cough and anosmia in the IVM-treated patients, but no differences in the patient-days for fever, general malaise, headache, and nasal congestion. 	<p>Limitations:</p> <ul style="list-style-type: none"> • Small sample size • PCR is not a validated surrogate marker for clinical efficacy. • PCR cycle threshold values were higher for patients who received IVM than those who received placebo at some time points, but these comparisons are not statistically significant. • Symptom results were not a prespecified outcome and are of unclear statistical and clinical significance. <p>Interpretation:</p> <ul style="list-style-type: none"> • Patients who received IVM showed no difference in viral clearance compared to those who received placebo.

Study Design	Methods	Results	Limitations and Interpretation
Effect of Early Treatment With Ivermectin Versus Placebo on Viral Load, Symptoms, and Humoral Response in Patients With Mild COVID-19⁴, continued			
			<ul style="list-style-type: none"> The small sample size and large number of comparisons make it difficult to assess the clinical efficacy of IVM in this population.
Ivermectin Plus Doxycycline Plus Standard Therapy Versus Standard Therapy Alone in Patients With Mild to Moderate COVID-19⁵			
<p>Randomized, unblinded, single-center study of patients with laboratory-confirmed SARS-CoV-2 infection in Baghdad, Iran (n = 140)</p> <p><i>This is a preliminary report that has not yet been peer reviewed.</i></p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> Diagnosis by clinical, radiological, and PCR testing Outpatients had mild or moderate COVID-19, while inpatients had severe and critical COVID-19. <p>Interventions:</p> <ul style="list-style-type: none"> IVM 200 µg/kg PO daily for 2 days. If patient required more time to recover, a third dose was given 7 days after the first dose, plus DOX 100 mg twice daily for 5–10 days plus standard therapy (based on clinical condition). Standard therapy was based on clinical condition and included AZM, acetaminophen, vitamin C, zinc, vitamin D3, dexamethasone 6 mg daily or methylprednisolone 40 mg twice daily if needed, and oxygen or mechanical ventilation if needed. All critically ill patients were assigned to receive IVM plus DOX. 	<p>Number of Participants:</p> <ul style="list-style-type: none"> IVM plus DOX plus standard therapy (n = 70) and standard therapy alone (n = 70) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> Median age was 50 years in IVM arm and 47 years in standard therapy arm. 50% of patients were male in IVM arm and 53% were male in standard therapy arm. In IVM arm, 48 patients had mild or moderate COVID-19, 11 had severe COVID-19, and 11 had critical COVID-19. In standard therapy arm, 48 patients had mild or moderate COVID-19, 22 had severe COVID-19, and no patients had critical COVID-19. <p>Outcomes:</p> <ul style="list-style-type: none"> Mean recovery time in IVM arm was 10.1 days (SD 5.3 days) vs. 17.9 days (SD 6.8 days) for standard therapy arm ($P < 0.0001$). This result was only significant for those with mild to moderate disease. Disease progression occurred in 3 of 70 patients (4.3%) in IVM arm and 7 of 70 (10.0%) in standard therapy arm ($P = 0.19$) 2 of 70 patients (2.85%) in IVM arm and 6 of 70 (8.57%) in standard therapy arm died ($P = 0.14$) 	<p>Limitations:</p> <ul style="list-style-type: none"> Not blinded Patient deaths prevent an accurate comparison of mean recovery time between arms in this study, and the authors did not account for competing mortality risks. Relies heavily on post hoc subgroup comparisons. Substantial imbalance in disease severity at baseline Authors noted that critical patients were not assigned to standard therapy arm; thus, the arms were not truly randomized. Unclear how many patients required corticosteroids. <p>Interpretation:</p> <ul style="list-style-type: none"> IVM may shorten the time to recovery for patients with mild or moderate disease, but the lack of control for competing mortality causes in the study limits the ability to interpret the results.

Study Design	Methods	Results	Limitations and Interpretation
Efficacy and Safety of Ivermectin Versus Hydroxychloroquine for Treatment of COVID-19⁶			
<p>Multicenter RCT that compared the use of IVM and HCQ in patients with mild, moderate, or severe COVID-19 in hospital settings (n = 400)</p> <p><i>This is a preliminary report that has not yet been peer reviewed.</i></p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Positive RT-PCR result • Mild, moderate, or severe cases of COVID-19 <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Contraindications for HCQ • Critical cases of COVID-19 • Chronic kidney, liver, or heart disease <p>Interventions</p> <p><i>All Patients:</i></p> <ul style="list-style-type: none"> • SOC, which included AZM 500 mg once daily for 6 days, vitamin C 1 gm once daily, zinc 50 mg once daily, lactoferrin 100 mg twice daily, acetylcysteine 200 mg 3 times daily, prophylactic or therapeutic anticoagulation if D-dimer >1,000, and paracetamol as needed. <p><i>Group 1 (Mild or Moderate) and Group 3 (Severe):</i></p> <ul style="list-style-type: none"> • IVM 400 µg/kg once daily for 4 days (maximum of IVM 24 mg per day) <p><i>Group 2 (Mild or Moderate) and Group 4 (Severe):</i></p> <ul style="list-style-type: none"> • HCQ 400 mg every 12 hours on Day 1, then HCQ 200 mg every 12 hours for 5 days <p>Primary Endpoints:</p> <ul style="list-style-type: none"> • Clinical laboratory improvement and/or 2 consecutive negative PCR results ≥48 hours apart • Length of hospital stay 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • All 4 arms (n = 100 in each arm) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Mean age was 53.8–59.6 years. • 67% to 72% of patients were male. • Fatigue and dyspnea reported in 36% to 38% of patients with mild or moderate disease and 86% to 88% of those with severe disease. <p>Primary Outcomes:</p> <ul style="list-style-type: none"> • In those with mild or moderate disease, patients who received IVM had significant differences in improvement compared to those who received HCQ (99% vs. 74%), progression of disease (1% vs. 22%), death (0% vs. 4%), and mean number of hospital days (5±1 vs. 15±8) (<i>P</i> < 0.001 for all parameters except death). • For those with severe disease, patients who received IVM had significant differences compared to those who received HCQ in improvement (94% vs. 50%), progression of disease (4% vs. 30%), death (2% vs. 20%), and mean number of hospital days (6±8 vs. 18±8) (<i>P</i> < 0.001 for all parameters). • For all patients, those treated with IVM had significant improvement in TLC, CRP, ferritin, D-dimer, and RT-PCR conversion days by Week 1 (<i>P</i> < 0.001) compared to those who received HCQ. • In addition to the markers listed above, patients with severe disease showed greater improvement in hemoglobin in IVM arm than in HCQ arm. 	<p>Limitations:</p> <ul style="list-style-type: none"> • Unclear whether the study team and patients were blinded. • The role of SOC therapy in clinical and laboratory responses is unknown. • Cannot rule out potential harm from HCQ. It is unknown whether using AZM plus HCQ could have led to worse outcomes. • No SOC alone group • Laboratory results are only reported after 1 week of treatment. Length of follow up for clinical outcomes and mortality is unclear. <p>Interpretation:</p> <ul style="list-style-type: none"> • Compared to those who received HCQ, IVM recipients had improved inflammatory markers and time to RT-PCR conversion after 1 week. Improvement in clinical status and decreased mortality was also observed in the IVM arm.

Study Design	Methods	Results	Limitations and Interpretation
Antiviral Effect of High-Dose Ivermectin in Adults with COVID-19⁷			
<p>Multicenter, randomized, open-label, blinded trial of hospitalized adults with mild to moderate COVID-19 (n = 45)</p> <p><i>This is a preliminary report that has not yet been peer-reviewed.</i></p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> Laboratory-confirmed SARS-CoV-2 infection Hospitalized with WHO Stage 3 to 5 COVID-19 ≤5 days of symptoms <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> Use of any agent with potential anti-SARS-CoV-2 activity or immunomodulators prior to enrollment Poorly controlled comorbidities <p>Interventions:</p> <ul style="list-style-type: none"> IVM 600 µg/kg once daily plus SOC for 5 days SOC for 5 days <p>Primary Endpoint:</p> <ul style="list-style-type: none"> VL reduction at Day 5. VL was quantified by NP swab at baseline, then at 24, 48, and 72 hours and Day 5. <p>PK Sampling:</p> <ul style="list-style-type: none"> Performed 4 hours after dose on Days 1, 2, 3, 5, and 7 to assess elimination 	<p>Number of Participants:</p> <ul style="list-style-type: none"> IVM (n = 30) and SOC (n = 15) After excluding patients with poor sample quality, those without a detectable VL at baseline, and those who withdrew, 32 patients (20 IVM, 12 SOC) were included in the viral efficacy analysis population. <p>Participant Characteristics:</p> <ul style="list-style-type: none"> Mean age was 40.9 years ± 12.5 years. 56% of patients were male. <p>Primary Outcomes:</p> <ul style="list-style-type: none"> Nonstatistically significant difference in baseline VL between arms. The baseline median VL was 3.74 log₁₀ copies/mL (range 2.8–5.79) in IVM arm and 5.59 log₁₀ copies/mL in SOC arm (P = 0.08). By Day 5, a similar magnitude of viral reduction was seen in both arms. <p>Other Outcomes:</p> <ul style="list-style-type: none"> A significant positive correlation was found after analysis of mean plasma IVM concentration in relation to VL reduction. Participants with higher IVM concentrations had greater reductions in VL (r 0.44; P < 0.04). This correlation was stronger when reduction in VL was related to the IVM exposure corrected by baseline VL (r 0.60; P < 0.004). Treated patients were divided into 2 groups based on IVM C_{max}: IVM >160 ng/mL (median of 202 ng/mL) and ≤160 ng/mL (median of 109 ng/mL). <ul style="list-style-type: none"> Median percentage of VL reduction by C_{max} concentration vs. control (P = 0.0096) was 72% (IQR 59% to 77%) in >160 ng/mL group (n = 9), 40% (IQR 21% to 46%) in ≤160 ng/mL group (n = 11), and 42% (IQR 31% to 73%) in SOC arm. Median viral decay rate (P = 0.041) was 0.64 d⁻¹ in >160 ng/mL group, 0.14 d⁻¹ in ≤160 ng/mL group, and 0.13 d⁻¹ in SOC arm. Percentages of AEs were similar between the arms (43% in IVM arm, 33% in SOC arm), and AEs were mostly mild. No correlation was found between IVM concentration and the occurrence of AEs. 	<p>Limitations:</p> <ul style="list-style-type: none"> Small sample size No clinical response data reported. The C_{max} level of 160 ng/mL used in the analysis appears to be arbitrary. <p>Interpretation:</p> <ul style="list-style-type: none"> Concentration-dependent virologic response was seen using a higher-than-usual dose of IVM (600 µg/kg vs. 200 or 400 µg/kg once daily), with minimal associated toxicities. The study results showed large interpatient variation of IVM C_{max}. Larger sample sizes are needed to further assess the safety and efficacy of using higher doses of IVM to treat COVID-19.

Study Design	Methods	Results	Limitations and Interpretation
Ivermectin as Adjunctive Therapy to Hospitalized Patients With COVID-19⁸			
<p>Randomized, double-blind, placebo-controlled multicenter Phase 2 clinical trial of hospitalized adults with mild to severe SARS-CoV-2 infection in 5 facilities in Iran (n = 180)</p> <p><i>This is a preliminary report that has not yet been peer-reviewed.</i></p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Symptoms suggestive of COVID-19 pneumonia, with chest CT compatible with mild to severe COVID-19 or positive RT-PCR result for SARS-CoV-2 <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Severe immunosuppression, malignancy, or chronic kidney disease • Pregnancy <p>Interventions:</p> <ul style="list-style-type: none"> • HCQ 200 mg/kg twice daily alone as SOC (standard arm) • SOC plus 1 of the following: <ul style="list-style-type: none"> • Placebo • Single dose of IVM 200 µg/kg • IVM 200 µg/kg on Days 1, 3, and 5 • Single dose of IVM 400 µg/kg • IVM 400 µg/kg on Day 1, then IVM 200 µg/kg on Days 3 and 5 <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Clinical recovery within 45 days of enrollment (defined as normal temp, respiratory rate, and SpO₂ >94% for 24 hours) 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • All 6 arms (n = 30 in each arm) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Average age was 56 years (range 45–67 years). • 50% of patients were male. • Disease stratification (based on CT findings): negative (1%), mild (14%), moderate (73%), and severe (12%) • Mean SpO₂ at baseline was 89%. <p>Primary Outcomes:</p> <ul style="list-style-type: none"> • Durations of hypoxemia ($P = 0.025$) and hospitalization ($P = 0.006$) were shorter in the IVM arms compared to placebo arm, and mortality was lower in the IVM arms ($P = 0.001$). • There was no difference in number of days of tachypnea ($P = 0.584$) or return to normal temperature ($P = 0.102$). • Significant differences in change from baseline to Day 5 in absolute lymphocyte count, platelet count, erythrocyte sedimentation rate, and CRP. • Higher mortality was reported in standard and placebo arm than IVM arms. 	<p>Limitations:</p> <ul style="list-style-type: none"> • Small study • Power estimation is confusing. • Mortality was not listed as the primary or secondary outcome. • It is unclear whether IVM patients also received HCQ. • It is unclear whether the between-group comparisons are between combined IVM group and placebo plus SOC. • Participants were stratified by disease severity based on CT findings. These categorizations are unclear and were not taken into account in outcome comparisons. • The post hoc grouping of randomized arms raises risk of false positive findings. <p>Interpretation:</p> <ul style="list-style-type: none"> • IVM appeared to improve laboratory outcomes and some clinical outcomes (shorter duration of hypoxemia and hospitalization) and lowered mortality. • The small size of the study, the unclear treatment arm assignments, and the lack of accounting of disease severity at baseline make it difficult to draw conclusions about the efficacy of using IVM to treat patients with mild COVID-19.

Study Design	Methods	Results	Limitations and Interpretation
Retrospective Analysis of Ivermectin in Hospitalized Patients With COVID-19^a			
<p>Retrospective analysis of consecutive patients with laboratory-confirmed SARS-CoV-2 infection who were admitted to 4 Florida hospitals (n = 276)</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Positive NP swab with SARS-CoV-2 RNA <p>Interventions:</p> <ul style="list-style-type: none"> • Single dose of IVM 200 µg/kg, repeated on Day 7 at the doctors' discretion; 90% percent of patients also received HCQ. • Usual care: 97% of patients received HCQ and most also received AZM. <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • All-cause, in-hospital mortality 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • IVM (n = 173; 160 participants received a single dose, 13 participants received a second dose) and usual care (n = 103) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Mean age was 60.2 years in IVM arm and 58.6 years in the usual care arm. • 51.4% of patients were male in IVM arm and 58.8% were male in usual care arm. • 56.6% of patients were Black in IVM arm and 51.4% were Black in usual care arm. <p>Outcomes:</p> <ul style="list-style-type: none"> • All-cause mortality was lower in IVM arm than in usual care arm (OR 0.27; 95% CI, 0.09–0.80; <i>P</i> = 0.03); the benefit appeared to be limited to the subgroup of patients with severe disease. • No difference in median length of hospital stay between arms (7 days for both) or proportion of mechanically ventilated patients who were successfully extubated (36% in IVM arm vs. 15% in usual care arm; <i>P</i> = 0.07). 	<p>Limitations:</p> <ul style="list-style-type: none"> • Not randomized • Little to no information on oxygen saturation or radiographic findings • Timing of therapeutic interventions was not standardized. • Ventilation and hospitalization duration analyses do not appear to account for death as a competing risk. • No virologic assessments were performed. <p>Interpretation:</p> <ul style="list-style-type: none"> • IVM use was associated with lower mortality than usual care. However, the limitations of this retrospective analysis make it difficult to draw conclusions about the efficacy of using IVM to treat patients with COVID-19.

Study Design	Methods	Results	Limitations and Interpretation
Observational Study on the Effectiveness of Hydroxychloroquine, Azithromycin, and Ivermectin Among Hospitalized Patients With COVID-19¹⁰			
<p>Retrospective cohort study of hospitalized adults with COVID-19 in Peru (n = 5,683)</p> <p><i>This is a preliminary report that has not yet been peer-reviewed.</i></p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged ≥18 years • Symptomatic • Laboratory-confirmed SARS-CoV-2 infection • No life-threatening illness at admission <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Required oxygen at admission • Use of tocilizumab, LPV/RTV, or RDV <p>Interventions:</p> <ul style="list-style-type: none"> • One of the following interventions administered within 48 hours of admission: <ul style="list-style-type: none"> • HCQ or CQ alone • IVM alone • AZM alone • HCQ or CQ plus AZM • IVM plus AZM • SOC (e.g., supportive care, antipyretics, hydration) <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • All-cause mortality <p>Secondary Endpoint:</p> <ul style="list-style-type: none"> • All-cause mortality and/or transfer to ICU 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • HCQ or CQ alone (n = 200), IVM alone (n = 203), AZM alone (n = 1,600), HCQ or CQ plus AZM (n = 692), IVM plus AZM (n = 358), and SOC (n = 2,630) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • 63% of patients were male. • Mean age was 59.4 years (range 18–104 years). • All patients had mild or moderate disease. <p>Outcomes:</p> <ul style="list-style-type: none"> • Median follow-up time was 7 days. Mortality rate was 18.9% at the end of follow up. • IVM alone was associated with increased risk of death and/or ICU transfer compared to SOC (wHR 1.58; 95% CI, 1.11–2.25). • IVM plus AZM did not have an effect on deaths or any secondary outcomes (all-cause death and/or ICU transfer, all-cause death and/or oxygen prescription) compared to SOC. • HCQ or CQ plus AZM was associated with a higher risk of death (wHR 1.84; 95% CI, 1.12–3.02), death and/or ICU transfer (wHR 1.49; 95% CI, 1.01–2.19), and death and/or oxygen prescription (wHR 1.70; 95% CI, 1.07–2.69) compared to SOC. 	<p>Limitations:</p> <ul style="list-style-type: none"> • Not randomized • Unclear whether all patients received IVM or other medications according to Peruvian guidelines referred to in the manuscript. • Dosing and timing of administration are unclear. <p>Interpretation:</p> <ul style="list-style-type: none"> • Compared to SOC, IVM alone was associated with increased risk of death and/or ICU admission. Using IVM in combination with AZM was not associated with effects on mortality, ICU transfer, or oxygen prescription compared to SOC.

Study Design	Methods	Results	Limitations and Interpretation
Retrospective Study of Ivermectin Versus Standard of Care in Patients With COVID-19¹¹			
<p>Retrospective study of consecutive adult patients hospitalized in Bangladesh with laboratory-confirmed SARS-CoV-2 infection (n = 248)</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged ≥18 years • Positive NP swab with SARS-CoV-2 RNA • “Free from any other serious pathological conditions” <p>Interventions:</p> <ul style="list-style-type: none"> • Single dose of IVM 12 mg within 24 hours of hospital admission • SOC <p>Primary Outcome:</p> <ul style="list-style-type: none"> • Not specified 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • IVM (n = 115) and SOC (n = 133) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Median age in IVM arm was 34 years; 70% of participants were male. • Median age in SOC arm was 35 years; 52% of participants were male. • All participants had mild or moderate disease. • 12% of participants had hypertension in both arms. • 17% of participants in IVM arm and 12% in SOC arm had diabetes mellitus. <p>Outcomes:</p> <ul style="list-style-type: none"> • Fewer patients in IVM arm had evidence of disease progression compared to SOC arm ($P < 0.001$): moderate respiratory distress (2.6% vs. 15.8%), pneumonia (0% vs. 9.8%), ischemic stroke (0% vs. 1.5%). • Fewer patients in IVM arm required intensive care management compared to SOC arm (0.9% vs. 8.8%; $P < 0.001$). • Fewer patients in IVM arm required antibiotic therapy (15.7% vs. 60.2%; $P < 0.001$) or supplemental oxygen (9.6% vs. 45.9%; $P < 0.001$) compared to SOC arm. • Shorter median duration of viral clearance in IVM arm compared to SOC arm (4 vs. 15 days; $P < 0.001$). • Shorter median duration of hospital stay in IVM arm compared to SOC arm (9 vs. 15 days; $P < 0.001$) • Lower mortality in IVM arm compared to SOC arm (0.9% vs. 6.8%; $P < 0.05$) 	<p>Limitations:</p> <ul style="list-style-type: none"> • Not randomized • Disease severity at admission was reported as mild or moderate, but 12% of patients in IVM arm and 9% in SOC arm had $SpO_2 < 94\%$ • Even though only 10% of patients developed pneumonia, 60% received antibiotics. • Possibility of harm from concomitant medications <p>Interpretation:</p> <ul style="list-style-type: none"> • Compared to SOC, IVM use was associated with faster rates of viral clearance and better clinical outcomes, including shorter hospital stay and lower mortality

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

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Lopinavir/Ritonavir and Other HIV Protease Inhibitors

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](https://www.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 $\mu\text{g/mL}$.
- After correcting for protein binding, trough levels would need to be approximately 60-fold to 120-fold higher to achieve the in vitro half-maximal effective concentration (EC_{50}) for SARS-CoV-2.

Limitations

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

Interpretation

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

Other Reviewed Studies

The Panel has reviewed other clinical studies that evaluated the use of protease inhibitors for the

treatment of COVID-19.^{6,8,9} These studies have limitations that make them less definitive and informative than larger randomized clinical trials. The Panel's summaries and interpretations of some of these studies are available in the [archived versions of the Guidelines](#).

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

Last Updated: April 21, 2021

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

Dosing Regimens <i>The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Remdesivir				
For Hospitalized Adult and Pediatric Patients (Aged ≥12 Years and Weighing ≥40 kg) <i>For Patients Who Are Not Mechanically Ventilated and/or on ECMO:</i> <ul style="list-style-type: none"> • RDV 200 mg IV over 30–120 minutes on Day 1, followed by RDV 100 mg IV on Day 2 through Day 5 	<ul style="list-style-type: none"> • 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. 	<ul style="list-style-type: none"> • Infusion reactions • Renal function, hepatic function, and prothrombin time should be monitored before and during treatment as clinically indicated. • RDV is not recommended if eGFR is <30 mL/min. 	<ul style="list-style-type: none"> • Clinical drug-drug interaction studies of RDV have not been conducted. • In vitro, RDV is a substrate of CYP3A4, OATP1B1, and P-gp and an inhibitor of CYP3A4, OATP1B1, OATP1B3, and MATE1.¹ 	<ul style="list-style-type: none"> • RDV should be administered in a hospital or a health care setting that can provide a similar level of care to an inpatient hospital. • RDV is approved by the FDA for the treatment of COVID-19 in hospitalized adult and pediatric patients (aged ≥12 years and weighing ≥40 kg). • An EUAA is available for hospitalized pediatric patients weighing 3.5 kg to <40 kg or aged <12 years and weighing ≥3.5 kg.

Dosing Regimens <i>The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Remdesivir , continued				
<ul style="list-style-type: none"> • Treatment may be extended to up to 10 days in patients who do not show clinical improvement after 5 days of therapy. <p><i>For Mechanically Ventilated Patients and/or Patients on ECMO:</i></p> <ul style="list-style-type: none"> • RDV 200 mg IV over 30–120 minutes on Day 1, followed by RDV 100 mg IV on Day 2 through Day 10 <p>Suggested Dose in EUA^a for Hospitalized Pediatric Patients Weighing 3.5 kg to <40 kg or Aged <12 Years and Weighing ≥3.5 kg</p> <p><i>For Patients Weighing 3.5 kg to <40 kg:</i></p> <ul style="list-style-type: none"> • RDV 5 mg/kg IV over 30–120 minutes on Day 1, followed by RDV 2.5 mg/kg IV once daily starting on Day 2 • For patients who are not mechanically ventilated and/or on ECMO, the recommended treatment duration is 5 days. If patients have not shown clinical improvement after 5 days of therapy, treatment may be extended to up to 10 days. • For mechanically ventilated patients and/or patients on ECMO, the recommended treatment duration is 10 days. <p><i>For Patients Aged <12 Years and Weighing ≥40 kg:</i></p> <ul style="list-style-type: none"> • Same dose as for adults and children aged ≥12 years and weighing >40 kg 	<ul style="list-style-type: none"> • 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. 	<ul style="list-style-type: none"> • RDV may need to be discontinued if ALT level increases to >10 times the ULN and should be discontinued if there is an increase in ALT level and signs or symptoms of liver inflammation are observed.¹ 	<ul style="list-style-type: none"> • Minimal to no reduction in RDV exposure is expected when RDV is coadministered with dexamethasone (Gilead Sciences, written communication, July 2020). • CQ or HCQ may decrease the antiviral activity of RDV; coadministration of these drugs is not recommended.¹ • No significant interaction is expected between RDV and oseltamivir or baloxavir (Gilead Sciences, personal and written communications, August and September 2020). 	<ul style="list-style-type: none"> • A list of clinical trials is available here: Remdesivir

Dosing Regimens <i>The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Ivermectin				
Adults: <ul style="list-style-type: none"> The dose most commonly used in clinical trials is IVM 0.2–0.6 mg/kg given as a single dose or as a once-daily dose for up to 5 days. 	<ul style="list-style-type: none"> Generally well tolerated Dizziness Pruritis GI effects (e.g., nausea, diarrhea) Neurological AEs have been reported with the use of IVM for the treatment of parasitic diseases, but it is not clear whether these AEs were caused by IVM or the underlying conditions. 	<ul style="list-style-type: none"> Monitor for potential AEs. 	<ul style="list-style-type: none"> Minor CYP3A4 substrate P-gp substrate 	<ul style="list-style-type: none"> Generally given on an empty stomach with water; however, administering IVM with food increases its bioavailability.² A list of clinical trials is available here: Ivermectin

^a The FDA EUA permits the emergency use of RDV for the treatment of suspected COVID-19 or laboratory-confirmed SARS-CoV-2 infection in hospitalized pediatric patients weighing 3.5 kg to <40 kg or aged <12 years and weighing ≥3.5 kg.³

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

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Anti-SARS-CoV-2 Antibody Products

Last Updated: April 21, 2021

Summary Recommendations

Anti-SARS-CoV-2 Monoclonal Antibodies

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using one of the following anti-SARS-CoV-2 monoclonal antibody combinations (listed in alphabetical order) to treat outpatients with mild to moderate COVID-19 who are at high risk of clinical progression, as defined by the Emergency Use Authorization (EUA) criteria for the products:
 - **Bamlanivimab 700 mg plus etesevimab 1,400 mg (AIIa); or**
 - **Casirivimab 1,200 mg plus imdevimab 1,200 mg (AIIa).**
- Treatment should be started as soon as possible after the patient receives a positive result on a SARS-CoV-2 antigen or nucleic acid amplification test and within 10 days of symptom onset.
- There are no comparative data to determine whether there are differences in clinical efficacy or safety between bamlanivimab plus etesevimab and casirivimab plus imdevimab.
 - There are SARS-CoV-2 variants, particularly those that contain the mutation E484K, that reduce the virus' susceptibility to bamlanivimab and, to a lesser extent, casirivimab and etesevimab in vitro; however, the clinical impact of these mutations is not known.
 - In regions where SARS-CoV-2 variants with reduced in vitro susceptibility to bamlanivimab plus etesevimab are common, some Panel members would preferentially use casirivimab plus imdevimab while acknowledging that it is not known whether in vitro susceptibility data correlate with clinical outcomes.
- The Panel **recommends against** the use of **anti-SARS-CoV-2 monoclonal antibodies** for patients who are hospitalized because of COVID-19, except in a clinical trial (**AIIa**). However, their use should be considered for persons with mild to moderate COVID-19 who are hospitalized for a reason other than COVID-19 but who otherwise meet the EUA criteria.

COVID-19 Convalescent Plasma

- The Panel **recommends against** the use of **low-titer COVID-19 convalescent plasma** for the treatment of COVID-19 (**AIIb**). Low-titer COVID-19 convalescent plasma is no longer authorized through the convalescent plasma EUA.
- For hospitalized patients with COVID-19 who do not have impaired immunity:
 - The Panel **recommends against** the use of **COVID-19 convalescent plasma** for the treatment of COVID-19 in mechanically ventilated patients (**AI**).
 - The Panel **recommends against** the use of **high-titer COVID-19 convalescent plasma** for the treatment of COVID-19 in hospitalized patients who do not require mechanical ventilation, except in a clinical trial (**AI**).
- For hospitalized patients with COVID-19 who have impaired immunity:
 - There are insufficient data for the Panel to recommend either for or against the use of high-titer COVID-19 convalescent plasma for the treatment of COVID-19.
- For nonhospitalized patients with COVID-19:
 - There are insufficient data for the Panel to recommend either for or against the use of high-titer COVID-19 convalescent plasma for the treatment of COVID-19 in patients who are not hospitalized.

Anti-SARS-CoV-2 Specific Immunoglobulin

- There are insufficient data for the Panel to recommend either for or against the use of anti-SARS-CoV-2 specific immunoglobulin 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: April 21, 2021

Background

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

Many individuals with COVID-19 produce neutralizing antibodies to SARS-CoV-2 about 10 days after disease onset, with higher antibody levels observed in those with severe disease.² The neutralizing activity of COVID-19 patients' plasma was correlated with the magnitude of antibody responses to SARS-CoV-2 S and N proteins. Monoclonal antibodies targeting the S protein have the potential to prevent SARS-CoV-2 infection and to alleviate symptoms and limit progression to severe disease in patients with mild to moderate COVID-19, particularly in those who have not yet developed an endogenous antibody response.³

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

Bamlanivimab (also known as LY-CoV555 and LY3819253) is a neutralizing monoclonal antibody that targets the RBD of the S protein of SARS-CoV-2. Etesevimab (also known as LY-CoV016 and LY3832479) is another neutralizing monoclonal antibody that binds to a different but overlapping epitope in the RBD of the SARS-CoV-2 S protein. Casirivimab (previously REGN10933) and imdevimab (previously REGN10987) are recombinant human monoclonal antibodies that bind to nonoverlapping epitopes of the S protein RBD of SARS-CoV-2.

Two combination products, bamlanivimab plus etesevimab and casirivimab plus imdevimab, are available through Food and Drug Administration (FDA) Emergency Use Authorizations (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. The issuance of an EUA does not constitute FDA approval. Because of an increasing number of reports of SARS-CoV-2 variants that are resistant to bamlanivimab alone, FDA has recently revoked the EUA for bamlanivimab, and the product will no longer be distributed in the United States.⁴

Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using one of the following anti-SARS-CoV-2 monoclonal antibody combinations (listed in alphabetical order) to treat outpatients with mild to moderate COVID-19 who are at high risk of clinical progression, as defined by the EUA criteria:
 - **Bamlanivimab 700 mg plus etesevimab 1,400 mg (AIIa); or**
 - **Casirivimab 1,200 mg plus imdevimab 1,200 mg (AIIa).**
- Treatment should be started as soon as possible after the patient receives a positive result on a SARS-CoV-2 antigen or nucleic acid amplification test (NAAT) and within 10 days of symptom onset.

- There are SARS-CoV-2 variants, particularly those that contain the mutation E484K (see below), that reduce the virus' susceptibility to bamlanivimab and, to a lesser extent, casirivimab and etesevimab in vitro; however, the clinical impact of these mutations is not known.
- In regions where SARS-CoV-2 variants with reduced in vitro susceptibility to bamlanivimab plus etesevimab are common, some Panel members would preferentially use casirivimab plus imdevimab while acknowledging that it is not known whether in vitro susceptibility data correlate with clinical outcomes.
- The Panel **recommends against** the use of **anti-SARS-CoV-2 monoclonal antibodies** for patients who are hospitalized because of COVID-19, except in a clinical trial (**AIIa**). However, their use should be considered for persons with mild to moderate COVID-19 who are hospitalized for a reason other than COVID-19 but who otherwise meet the EUA criteria.

For additional information on the rationale for the Panel's recommendations regarding anti-SARS-CoV-2 monoclonal antibodies for nonhospitalized patients with mild to moderate COVID-19, see [Therapeutic Management of Patients with COVID-19](#).

SARS-CoV-2 Variants of Concern or Interest and Their Susceptibility to Anti-SARS-CoV-2 Monoclonal Antibodies

In laboratory studies, some SARS-CoV-2 variants of concern or interest that harbor certain mutations have markedly reduced susceptibility to bamlanivimab and may have lower sensitivity to etesevimab and casirivimab.⁵ However, the impact of these mutations on the clinical response to anti-SARS-CoV-2 monoclonal antibody combinations is uncertain, and the prevalence of these variants in different regions may vary. Of note:

- The B.1.1.7 variant of concern, which is increasing in frequency in the United States, retains in vitro susceptibility to the anti-SARS-CoV-2 monoclonal antibodies that are currently available through EUAs.^{6,7}
- The B.1.351 variant of concern has been infrequently detected among SARS-CoV-2 samples sequenced in the United States to date. This variant includes the E484K mutation, which results in a marked reduction in in vitro susceptibility to bamlanivimab.^{8,9} In vitro studies suggest that bamlanivimab plus etesevimab has markedly reduced activity against the B.1.351 variant.⁶ In vitro studies also suggest that the K417N mutation, which is present in the B.1.351 variant along with the E484K mutation, reduces casirivimab activity, although the combination of casirivimab and imdevimab appears to retain activity.⁷
- The P.1 variant of concern has been infrequently detected among SARS-CoV-2 samples sequenced in the United States to date. This variant includes the E484K mutation, which results in a marked reduction in in vitro susceptibility to bamlanivimab.^{6,10} In vitro studies suggest that bamlanivimab plus etesevimab also has markedly reduced activity against the P.1 variant.^{6,8,10} In vitro studies also suggest that the K417T mutation, which is present in the P.1 variant along with the E484K mutation, reduces casirivimab activity, although the combination of casirivimab and imdevimab appears to retain activity.⁷
- The B.1.429/B.1.427 variants of concern (also called 20C/CAL.20C) that are circulating in parts of the United States, including California, Arizona, and Nevada, have the L452R mutation. This mutation is associated with a marked reduction in in vitro susceptibility to bamlanivimab. There appears to be a modest in vitro decrease in susceptibility to the combination of bamlanivimab and etesevimab, although the clinical implications of this finding are not known.⁶
- The B.1.526 variant of interest is circulating in parts of the United States, such as New York.

It commonly has the E484K mutation, which is associated with a marked reduction in in vitro susceptibility to bamlanivimab. There appears to also be reduced in vitro susceptibility to the combination of bamlanivimab and etesevimab, although the clinical implications of this finding are not known.⁶ In vitro studies suggest that the E484K mutation may reduce casirivimab activity, although the combination of casirivimab and imdevimab appears to retain activity.⁷

Ongoing [population-based genomic surveillance](#) of the types and frequencies of circulating SARS-CoV-2 variants, as well as studies on the susceptibility of different variants to available anti-SARS-CoV-2 monoclonal antibodies, will be important in defining the utility of specific monoclonal antibodies in the future.

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

The FDA EUAs do not authorize the use of anti-SARS-CoV-2 monoclonal antibodies for patients who are hospitalized for COVID-19 or for the following patients:

- 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, because of COVID-19, require an increase in oxygen flow rate from baseline.

The FDA EUAs do permit the use of these monoclonal antibodies for patients who are hospitalized for an indication other than COVID-19 provided they have mild to moderate COVID-19 and are at high risk for progressing to severe disease and/or hospitalization.^{11,12}

Anti-SARS-CoV-2 monoclonal antibodies 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 antibodies provide clinical benefits in people with B-cell immunodeficiency or other immunodeficiencies.

Anti-SARS-CoV-2 monoclonal antibodies have not been shown to be beneficial in hospitalized patients with severe COVID-19.^{7,12} A substudy of A Multicenter, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients With COVID-19 (ACTIV-3) randomized patients hospitalized with COVID-19 to receive bamlanivimab 7,000 mg or placebo, each in addition to remdesivir. On October 26, 2020, following a prespecified interim futility analysis, enrollment into this study was stopped due to lack of clinical benefit.¹³ Among 314 hospitalized adults (163 in the bamlanivimab arm and 151 in the placebo arm), pulmonary outcomes were similar at Day 5 (OR of being in a more favorable category in the bamlanivimab arm than in the placebo arm 0.85; 95% CI, 0.56–1.29; $P = 0.45$). The time to hospital discharge was also similar in the two arms (rate ratio 0.97; 95% CI, 0.78–1.20).¹⁴

Clinical Trial Data

See [Table 3a](#) for information on the clinical trials evaluating the safety and efficacy of anti-SARS-CoV-2 monoclonal antibodies.

Monitoring

- These anti-SARS-CoV-2 monoclonal antibodies are to be given as intravenous infusions and should only be administered in health care settings by qualified health care providers who have immediate access to medications to treat severe infusion reactions and to emergency medical services.

- Patients should be monitored during the infusion and for at least 1 hour after the infusion is completed.
- No dosage adjustments are required for body weight, renal impairment, or mild hepatic impairment.

Adverse Effects

- In the Phase 2 Blocking Viral Attachment and Cell Entry with SARS-CoV-2 Neutralizing Antibodies (BLAZE-1) trial, the most common adverse events associated with bamlanivimab were nausea, diarrhea, dizziness, headache, pruritis, and vomiting. The safety profile of bamlanivimab at all three doses was reportedly like that of the placebo.
- According to the EUA fact sheet for bamlanivimab plus etesevimab, the following adverse events were reported: nausea, dizziness, rash, pruritis, and pyrexia. In the Phase 3 BLAZE-1 study, 1% of the participants experienced hypersensitivity events, including infusion-related reactions, rash, and pruritis. All events resolved.
- Hypersensitivity, including anaphylaxis and infusion reactions, may occur. According to the EUA for bamlanivimab, among >850 participants in ongoing trials who have received bamlanivimab, one anaphylactic reaction and one serious infusion-related reaction occurred, and both required treatment, which in one case included epinephrine.
- According to the EUA fact sheet for casirivimab plus imdevimab, among the 533 participants who received casirivimab plus imdevimab in the R10933-10987-COV-2067 trial, one participant had an anaphylaxis reaction that required treatment with epinephrine, and four participants who received casirivimab 4,000 mg plus imdevimab 4,000 mg had an infusion reaction of grade 2 severity or higher, which, in two cases, resulted in permanent discontinuation of the infusion.

Drug-Drug Interactions

- Drug-drug interactions are unlikely between bamlanivimab plus etesevimab or casirivimab plus imdevimab and medications that are renally excreted or that are cytochrome P450 substrates, inhibitors, or inducers.
- Please see [Table 3c](#) for more information.

Vaccination

- SARS-CoV-2 vaccination should be deferred for ≥ 90 days in people who have received anti-SARS-CoV-2 monoclonal antibodies. This is a precautionary measure, as the antibody treatment may interfere with vaccine-induced immune responses.¹⁵
- For people who develop COVID-19 after receiving SARS-CoV-2 vaccination, prior vaccination should not affect treatment decisions, including the use of and timing of treatment with monoclonal antibodies.¹⁵

Considerations in Pregnancy

- As immunoglobulin (Ig) G monoclonal antibodies, bamlanivimab plus etesevimab, casirivimab plus imdevimab, and bamlanivimab alone would be expected to cross the placenta. There are no available data on the use of these anti-SARS-CoV-2 monoclonal antibodies during pregnancy; however, IgG products are generally not withheld because of pregnancy when their use is indicated.
- Anti-SARS-CoV-2 monoclonal antibodies should not be withheld from a pregnant individual with

COVID-19 who has a condition that poses a high risk of progression to severe COVID-19, and the patient and provider determine that the potential benefit of the drug outweighs the potential risk (see the EUA criteria for the use of these products below).

- Inclusion of pregnant people in clinical trials should be encouraged to inform decisions on whether to use anti-SARS-CoV-2 monoclonal antibody therapy in this population.

Considerations in Children

- There are insufficient pediatric data 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 for nonhospitalized children who meet EUA criteria, especially those who meet more than one criterion or are aged ≥ 16 years, on a case-by-case basis in consultation with a pediatric infectious disease specialist. Additional guidance on the use of anti-SARS-CoV-2 monoclonal antibodies for the treatment of COVID-19 in children is provided in a recent publication endorsed by the Pediatric Infectious Diseases Society.¹⁶
- Most children with mild or moderate COVID-19, even those with risk factors specified in the EUAs for bamlanivimab plus etesevimab or casirivimab plus imdevimab, will not progress to more severe illness and will recover without specific therapy.
- Risk factors for hospitalization have not been as clearly defined in children with COVID-19 as in adults with the disease, making it difficult to identify those children at the highest risk of hospitalization and those who would be likely to benefit from monoclonal antibody therapy.
- Additional data on clinical outcomes in children who receive monoclonal antibodies for the treatment of COVID-19, including in those with specific risk factors, are needed.
- Please see [Special Considerations in Children](#) for more information.

Clinical Trials

- Health care providers are encouraged to discuss participation in anti-SARS-CoV-2 monoclonal antibody clinical trials with patients who have mild to moderate COVID-19.

Drug Availability

- Bamlanivimab plus etesevimab and casirivimab plus imdevimab are available through FDA EUAs.¹⁷
- Given the possibility of a limited supply of bamlanivimab plus etesevimab and casirivimab plus imdevimab, as well as challenges of distributing and administering the drugs, patients who are at highest risk for COVID-19 progression based on the EUA criteria should have priority access to the drugs.^{18,19}
- Efforts should be made to ensure that communities most affected by COVID-19 have equitable access to these monoclonal antibodies.

High-Risk Criteria in the Emergency Use Authorizations for Anti-SARS-CoV-2 Monoclonal Antibodies

The FDA EUAs for all available anti-SARS-CoV-2 monoclonal antibodies and combinations have the same criteria for use: they allow for the use of the monoclonal antibodies for the treatment of COVID-19 in nonhospitalized adults and children aged ≥ 12 years and weighing ≥ 40 kg who are at high risk for progressing to severe COVID-19 and/or hospitalization.

High-risk individuals as specified in the EUA are those who meet at least one of the following criteria:

- Body mass index (BMI) ≥ 35
- Chronic kidney disease
- Diabetes mellitus
- Immunocompromising condition
- Currently receiving immunosuppressive treatment
- Aged ≥ 65 years
- Aged ≥ 55 years and have:
 - Cardiovascular disease, *or*
 - Hypertension, *or*
 - Chronic obstructive pulmonary disease or another chronic respiratory disease.
- Aged 12 to 17 years and have:
 - BMI ≥ 85 th percentile for their age and gender based on the [Centers for Disease Control and Prevention growth charts](#); *or*
 - Sickle cell disease; *or*
 - Congenital or acquired heart disease; *or*
 - Neurodevelopmental disorders (e.g., cerebral palsy); *or*
 - A medical-related technological dependence that is not related to COVID-19 (e.g., tracheostomy, gastrostomy, positive pressure ventilation); *or*
 - Asthma or a reactive airway or other chronic respiratory disease that requires daily medication for control.

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

Last Updated: April 21, 2021

Study Design	Methods	Results	Limitations and Interpretation
Bamlanivimab Plus Etesevimab Versus Placebo in Outpatients With COVID-19 (BLAZE-1)^{1,2}			
<p>Double-blind, Phase 3 RCT in outpatients with mild to moderate COVID-19 who are at high risk for progressing to severe COVID-19 and/or hospitalization as defined in the BAM plus ETE EUA (n = 1,035)</p> <p>Note: These data are from the FDA EUA for BAM plus ETE and from a conference abstract presentation.</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged ≥ 12 years • Not currently hospitalized • ≥ 1 mild or moderate COVID-19 symptom • At high risk for progressing to severe COVID-19 and/or hospitalization <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • SpO₂ $\leq 93\%$ on room air, <i>or</i> • Respiratory rate ≥ 30 breaths/min, <i>or</i> • Heart rate ≥ 125 bpm <p>Interventions:</p> <ul style="list-style-type: none"> • Single IV infusion of: <ul style="list-style-type: none"> • BAM 2,800 mg plus ETE 2,800 mg, <i>or</i> • Placebo • Administered within 3 days after receiving a positive result on a SARS-CoV-2 virologic test <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Proportion of participants with COVID-19 related hospitalization (defined as ≥ 24 hours of acute care) or death by any cause by Day 29 <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> • Proportion of participants with persistently high VL (defined as SARS-CoV-2 level $> 5.27 \log_{10}$ copies/mL) at Day 7 • Mean change in VL from baseline to Days 3, 5, and 7 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • BAM plus ETE (n = 518) and placebo (n = 517) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Median age was 56 years; 31% of the participants were aged ≥ 65 years. • 48% of the participants were men. • 87% of the participants were White; 8% were Black or African American; and 29% were Hispanic/Latinx. • Mean duration of symptoms was 4 days. • 77% of the participants had mild COVID-19. <p>Primary Outcomes:</p> <ul style="list-style-type: none"> • Proportion of participants with COVID-19 related hospitalization or death by any cause by Day 29: <ul style="list-style-type: none"> • 11 of 518 participants (2.1%) in the BAM plus ETE arm vs. 36 of 517 (7.0%) in the placebo arm ($P = 0.0004$) • Relative reduction: 70% • Proportion of participants who had died from any cause by Day 29: <ul style="list-style-type: none"> • 0 of 518 participants (0%) in the BAM plus ETE arm vs. 10 of 517 (1.9%) in the placebo arm ($P < 0.001$). <p>Secondary Outcome:</p> <ul style="list-style-type: none"> • The proportion of participants with persistently high VLs at Day 7 was 10% in the BAM plus ETE arm vs. 29% in the placebo arm ($P < 0.000001$). 	<p>Limitation:</p> <ul style="list-style-type: none"> • Trial data have not yet been peer reviewed and published. <p>Interpretation:</p> <ul style="list-style-type: none"> • There was a 5% absolute reduction and a 70% relative reduction in COVID-19-related hospitalizations or deaths from any cause among the participants who received BAM plus ETE compared to those who received placebo. • Data are for a BAM plus ETE dose which is not the dose authorized in the EUA.

Study Design	Methods	Results	Limitations and Interpretation
REGN10933 and REGN10987 (Casirivimab Plus Imdevimab) Versus Placebo in Outpatients with COVID-19 (Modified Full Analysis of R10933-10987-COV-2067 Trial)³			
<p>Double-blind, Phase 3 RCT in outpatients with mild to moderate COVID-19 (n = 4,180 for modified full analysis subset of the Phase 3 trial)</p> <p><i>These data are publicly available but have not been peer reviewed or published.</i></p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> Onset of COVID-19 symptoms ≤ 7 days before randomization SARS-CoV-2 PCR positive at baseline Criteria only for the modified full analysis: <ul style="list-style-type: none"> Aged ≥ 18 years ≥ 1 risk factor for severe COVID-19 <p>Interventions:</p> <ul style="list-style-type: none"> Single IV infusion of: <ul style="list-style-type: none"> CAS 600 mg plus IMD 600 mg, CAS 1,200 mg plus IMD 1,200 mg, <i>or</i> Placebo <p>Endpoint:</p> <ul style="list-style-type: none"> Proportion of participants with COVID-19-related hospitalization or all-cause death through Day 29 	<p>Number of Participants:</p> <ul style="list-style-type: none"> CAS 600 mg plus IMD 600 mg (n = 736) vs. placebo (n = 748) CAS 1,200 mg plus IMD 1,200 mg (n = 1,355) vs. placebo (n = 1,341) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> Median age was 50 years. 35% of the participants were Hispanic/Latinx and 5% were Black or African American. Median duration of symptoms prior to enrollment was 3 days (IQR 2–5 days).⁴ <p>Outcomes:</p> <ul style="list-style-type: none"> Percentage of participants with COVID-19-related hospitalization or all-cause death through Day 29 (based on participants in the modified cohort): <ul style="list-style-type: none"> 7 of 736 (1.0%) in the CAS 600 mg plus IMD 600 mg arm vs. 24 of 748 (3.2%) in the placebo arm ($P = 0.0024$) 18 of 1,355 (1.3%) in the CAS 1,200 mg plus IMD 1,200 mg arm vs. 62 of 1,341 (4.6%) in the placebo arm ($P < 0.0001$) Percentage of participants who died (based on all study participants): <ul style="list-style-type: none"> 1 of 827 (0.1%) in the CAS 600 mg plus IMD 600 mg arm 1 of 1,849 (0.05%) in the CAS 1,200 mg plus IMD 1,200 mg arm 5 of 1,843 (0.3%) in the placebo arm 	<p>Limitations:</p> <ul style="list-style-type: none"> The modified full analysis data have not been peer reviewed or published. Details of the study design, follow-up, and full methods are limited. <p>Interpretation:</p> <ul style="list-style-type: none"> There was a 2.2% absolute reduction and a 70% relative risk reduction in COVID-19-related hospitalizations or all-cause deaths in participants who received CAS 600 mg plus IMD 600 mg compared to those who received placebo. There was a 3.3% absolute reduction and a 71% relative risk reduction in COVID-19 related hospitalizations and all-cause deaths in participants who received CAS 1,200 mg plus IMD 1,200 mg compared to those who received placebo.

Study Design	Methods	Results	Limitations and Interpretation
REGN10933 and REGN10987 (Casirivimab Plus Imdevimab) Versus Placebo in Outpatients With COVID-19 (R10933-10987-COV-2067 Trial)⁵			
<p>Double-blind, Phase 1 and 2 RCT in outpatients with mild to moderate COVID-19 (n = 799)</p> <p>Note: These data are from the FDA EUA for CAS plus IMD.</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> Onset of COVID-19 symptoms ≤ 7 days before randomization SpO₂ $\geq 93\%$ on room air <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> Hospitalization before or at randomization due to COVID-19 Prior, current, or planned future use of any of the treatments specified in the protocol (e.g., COVID-19 CP, IVIG for any indication) <p>Interventions:</p> <ul style="list-style-type: none"> Single IV infusion of: <ul style="list-style-type: none"> CAS plus IMD 2,400 mg (CAS 1,200 mg and IMD 1,200 mg), CAS plus IMD 8,000 mg (CAS 4,000 mg and IMD 4,000 mg), <i>or</i> Placebo Administered ≤ 3 days after receiving a positive result on a SARS-CoV-2 virologic test <p>Primary Endpoint:</p> <ul style="list-style-type: none"> TWA change in NP VL from baseline to Day 7 <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> COVID-19-related medical visits including hospitalization or ED, urgent care, or physician office/telemedicine visit within 28 days of treatment Safety Symptom improvement 	<p>Number of Participants:</p> <ul style="list-style-type: none"> CAS plus IMD (n = 533): <ul style="list-style-type: none"> CAS plus IMD 2,400 mg (n = 266) CAS plus IMD 8,000 mg (n = 267) Placebo (n = 266) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> Median age was 42 years; 7% of the participants were aged ≥ 65 years. 34% of the participants had risk factors for severe COVID-19. Median duration of symptoms was 3 days. <p>Primary Outcome:</p> <ul style="list-style-type: none"> The primary endpoint was evaluated in the modified full analysis set of participants with detectable virus at baseline (n = 665). TWA change in NP VL at Day 7 was greater among the CAS plus IMD-treated participants overall than among the placebo-treated participants ($-0.36 \log_{10}$ copies/mL; $P < 0.0001$). <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> The proportion of participants who had COVID-19-related medical visits within 28 days of treatment was lower in the combined CAS plus IMD arms than in the placebo arm: <ul style="list-style-type: none"> Combined CAS plus IMD arms: 2.8% of patients Placebo arm: 6.5% of patients In a post hoc analysis, percentage of participants who were hospitalized or had a medical visit within 28 days of treatment: <ul style="list-style-type: none"> All CAS plus IMD doses: 8 of 434 (2%) CAS plus IMD 2,400 mg: 4 of 215 (2%) CAS plus IMD 8,000 mg: 4 of 219 (2%) Placebo: 10 of 231 (4%) 	<p>Limitations:</p> <ul style="list-style-type: none"> Relatively small number of participants in each arm Low number of hospitalizations or ED visits <p>Interpretation:</p> <ul style="list-style-type: none"> Compared to placebo, a single infusion of CAS plus IMD showed a reduction in NP VL at Day 7 among outpatients with mild or moderate COVID-19. The combined hospitalization or ED visit rate was lower in the CAS plus IMD arms than in the placebo arm, but the number of events in each arm was small. Because of the small number of clinical events, it is difficult to draw definitive conclusions about the clinical benefit of CAS plus IMD from this study. Additional data from a follow-up trial have been reported but remain unpublished.

Study Design	Methods	Results	Limitations and Interpretation
REGN10933 and REGN10987 (Casirivimab Plus Imdevimab) Versus Placebo in Outpatients With COVID-19 (R10933-10987-COV-2067 Trial)⁵, continued			
		<ul style="list-style-type: none"> • In a post hoc analysis, percentage of participants at high-risk for progression to severe COVID-19 and/or hospitalization who required hospitalization or ED visit: <ul style="list-style-type: none"> • All CAS plus IMD doses: 4 of 151 (3%) • Placebo: 7 of 78 (9%) • Median time to symptom improvement: <ul style="list-style-type: none"> • Combined CAS plus IMD arms: 5 days • Placebo arm: 6 days • The safety profile of CAS plus IMD was similar to the profile for the placebo. • 4 infusion related reactions of grade 2 severity or higher were reported in the CAS plus IMD 8,000 mg arm resulting in permanent discontinuation of the infusion in 2 participants; 1 participant had an anaphylactic reaction that resolved with treatment. 	
REGN10933 (Casirivimab) Plus REGN10987 (Imdevimab) Versus Placebo in Outpatients With COVID-19 (R10933-10987-COV-2067 Interim Analysis)⁶			
Note: The data presented in this published interim analysis represent a subset of participants described in the CAS plus IMD EUA (see study above).			
<p>Double-blind, Phase 1 and 2 RCT in outpatients with mild to moderate COVID-19 (n = 275)</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Onset of COVID-19 symptoms ≤ 7 days before randomization • SpO₂ $\geq 93\%$ on room air <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Hospitalization before or at randomization due to COVID-19 • Prior, current, or planned future use of any of the treatments specified in the protocol (e.g., COVID-19 CP, IVIG for any indication) <p>Interventions:</p> <ul style="list-style-type: none"> • Single IV infusion of: <ul style="list-style-type: none"> • CAS plus IMD 2,400 mg (CAS 1,200 mg and IMD 1,200 mg), 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • All CAS plus IMD doses (n = 182): <ul style="list-style-type: none"> • CAS plus IMD 2,400 mg (n = 92) • CAS plus IMD 8,000 mg (n = 90) • Placebo (n = 93) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Median age was 44 years (range 35–52 years). • Median time from symptom onset to randomization was 3 days. • Baseline serum antibody status: <ul style="list-style-type: none"> • Positive: 45% of participants • Negative: 41% of participants • Unknown: 14% of participants 	<p>Limitations:</p> <ul style="list-style-type: none"> • No formal hypothesis testing • Interim analysis • Relatively small number of participants in each arm • These data represent only a subset of participants described in the CAS plus IMD EUA (see the study above). • Low number of medical visits <p>Interpretation:</p> <ul style="list-style-type: none"> • Compared to placebo, a single infusion of CAS plus IMD showed a reduction in VL at Day 7 among outpatients with mild or moderate COVID-19.

Study Design	Methods	Results	Limitations and Interpretation
REGN10933 (Casirivimab) Plus REGN10987 (Imdevimab) Versus Placebo in Outpatients With COVID-19 (R10933-10987-COV-2067 Interim Analysis)⁶, continued			
	<ul style="list-style-type: none"> • CAS plus IMD 8,000 mg (CAS 4,000 mg and IMD 4,000 mg), <i>or</i> • Placebo • Administered ≤ 3 days after receiving a positive result on a SARS-CoV-2 virologic test <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • TWA change in NP VL from baseline to Day 7 in participants with negative serum antibody status at baseline <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> • COVID-19-related medical visits, including hospitalization or ED, urgent care, or physician office/telemedicine visit within 28 days of treatment • Safety • Symptom improvement 	<p>Primary Outcomes:</p> <ul style="list-style-type: none"> • Primary endpoint evaluated in modified full analysis set of participants with detectable virus at baseline (n = 221). • TWA change in NP VL at Day 7 was greater among the participants who received CAS plus IMD ($-1.74 \pm 0.11 \log_{10}$ copies/mL; 95% CI, -1.95 to -1.53) than among those who received placebo ($-1.34 \pm 0.13 \log_{10}$ copies/mL; 95% CI, -1.60 to -1.08). • Among the participants with a negative serum antibody status at baseline, TWA change in VL was greater among those who received CAS plus IMD ($-1.94 \pm 0.13 \log_{10}$ copies/mL; 95% CI, -2.20 to -1.67) than among those who received placebo ($-1.37 \pm 0.20 \log_{10}$ copies/mL; 95% CI, -1.76 to -0.98). <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> • The percentage of participants who had COVID-19-related medical visits within 28 days of treatment was lower in the CAS plus IMD arms than in the placebo arm: <ul style="list-style-type: none"> • All CAS plus IMD doses: 6 of 182 (3%) • Placebo: 6 of 93 (6%) • Among participants with negative serum antibody status at baseline, the percentage of those who had COVID-19-related medical visits within 28 days of treatment was lower in the CAS plus IMD arms: <ul style="list-style-type: none"> • All CAS plus IMD doses: 5 of 80 (6%) • Placebo: 5 of 33 (15%) • The safety profile of CAS plus IMD was similar to the profile of the placebo; 2 hypersensitivity or infusion related reactions of grade 2 severity or higher were reported in both the CAS plus IMD 8,000 mg arm and the placebo arm. • The mean half-life for both CAS and IMD antibodies ranged from 25–37 days. 	<ul style="list-style-type: none"> • The percentage of participants with medical visits was lower in the CAS plus IMD arms than in the placebo arm, but the number of events in each arm was small. • CAS plus IMD may have a greater effect in patients who are serum antibody negative but further investigation is needed. • Because of the small number of clinical events, it is difficult to draw definitive conclusions about the clinical benefit of CAS plus IMD from this study.

Key: ACTIV-3/TICO = A Multicenter, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients With COVID-19; AE = adverse event; BAM = bamlanivimab; BLAZE-1 = Blocking Viral Attachment and Cell Entry with SARS-CoV-2 Neutralizing Antibodies; BMI = body mass index; CAS = casirivimab; CP = convalescent plasma; ED = emergency department; ETE = etesevimab; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; IMD = imdevimab; IV = intravenous; IVIG = intravenous immunoglobulin; NP = nasopharyngeal; PCR = polymerase chain reaction; RCT = randomized controlled trial; RDV = remdesivir; SpO₂ = saturation of oxygen; TWA = time-weighted average; VL = viral load

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Convalescent Plasma

Last Updated: April 21, 2021

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

Recommendation

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

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

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

For Hospitalized Patients With COVID-19 Who Have Impaired Immunity

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

For Nonhospitalized Patients With COVID-19

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

Rationale for Recommendation

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Use of Convalescent Plasma in Nonhospitalized Patients With COVID-19

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

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

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

Clinical Data to Date

[Table 3b](#) includes a summary of key studies of convalescent plasma for the treatment of COVID-19.

Considerations in Pregnancy

The safety and efficacy of using COVID-19 convalescent plasma during pregnancy have not been

evaluated. Pathogen-specific immunoglobulins are used clinically during pregnancy to prevent infection from varicella zoster virus and rabies virus and have been used in clinical trials of congenital cytomegalovirus infection.³³ Some ongoing clinical trials that are evaluating COVID-19 convalescent plasma include pregnant individuals.³⁴

Considerations in Children

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

Adverse Effects

Available data suggest that serious adverse reactions following the administration of COVID-19 convalescent plasma are infrequent and consistent with the risks associated with plasma infusions for other indications. These risks include transfusion-transmitted infections (e.g., HIV, hepatitis B, hepatitis C), allergic reactions, anaphylactic reactions, febrile nonhemolytic reactions, transfusion-related acute lung injury, transfusion-associated circulatory overload, and hemolytic reactions. Hypothermia, metabolic complications, and post-transfusion purpura have also been described.^{21,35,36}

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

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

Product Availability

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

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

Clinical Trials

Randomized clinical trials that are evaluating convalescent plasma for the treatment of COVID-19 are underway. Please see [ClinicalTrials.gov](#) for the latest information.

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Table 3b. COVID-19 Convalescent Plasma: Selected Clinical Data

Last Updated: April 21, 2021

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

Study Design	Methods	Results	Limitations and Interpretation
Convalescent Plasma in Hospitalized Patients With COVID-19 (RECOVERY Trial)¹			
<p>Open-label, platform RCT evaluating potential treatments, including high-titer CP, in hospitalized patients with COVID-19 in the United Kingdom (n = 11,558)</p> <p><i>This is a preliminary report that has not yet been peer reviewed.</i></p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> Clinically suspected or laboratory-confirmed SARS-CoV-2 infection CP available at study site <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> CP contraindicated (e.g., known allergy to blood components) <p>Interventions:</p> <ul style="list-style-type: none"> One 275 mL (+/- 75 mL) unit of CP immediately and another unit the next day (≥12 hours after the first unit) CP was selected by sample to cut-off IgG SARS-CoV-2 spike protein ratio ≥6.0. Usual care <p>Primary Endpoint:</p> <ul style="list-style-type: none"> All-cause mortality at Day 28 <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> Time to hospital discharge Among patients not receiving IMV at randomization, receipt of IMV or death by Day 28 	<p>Number of Participants:</p> <ul style="list-style-type: none"> ITT analysis: CP (n = 5,795) and usual care (n = 5,763) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> Mean age was 63.5 years. 63% of patients in the CP arm and 66% in the usual care arm were men. 5% of patients in each arm were on IMV. At baseline, 52% of the patients in the CP arm and 48% in the usual care arm were SARS-CoV-2 antibody seropositive. 93% of the patients in the CP arm and 92% in the usual care arm received corticosteroids. <p>Outcomes:</p> <ul style="list-style-type: none"> No difference in 28-day mortality between the CP arm and the usual care arm (24% vs. 24%; rate ratio 1.00; 95% CI, 0.93–1.07). No difference in the proportion of patients discharged within 28 days (66% in CP arm vs. 67% in usual care arm; rate ratio 0.98; 95% CI, 0.94–1.03; <i>P</i> = 0.50). 28-day mortality rate ratio was consistent across prespecified patient subgroups, including subgroups by SARS-CoV-2 antibody presence at randomization. In particular, among patients without detectable SARS-CoV-2 antibodies, there was no evidence of a mortality difference between those who received CP and those who received usual care (32% vs. 34%; rate ratio 0.94; 95% CI, 0.84–1.06). Among those not receiving IMV at baseline, the percentage of patients who progressed to IMV or died was similar in the CP arm and the usual care arm (28% vs. 29%; rate ratio 0.99; 95% CI, 0.93–1.05; <i>P</i> = 0.79). Severe allergic reactions were rare (occurred in 16 patients in the CP arm and 2 in the usual care arm). 	<p>Limitations:</p> <ul style="list-style-type: none"> The study was not blinded. >90% of participants received corticosteroids. There is uncertainty about the effect of CP in hospitalized patients who do not require supplemental oxygen and for whom corticosteroids are not recommended. <p>Interpretation:</p> <ul style="list-style-type: none"> The trial did not demonstrate a benefit of CP in hospitalized patients with COVID-19.

Study Design	Methods	Results	Limitations and Interpretation
Convalescent Plasma in Hospitalized Adults With COVID-19 (PLACID Trial)²			
<p>Multicenter, open-label, Phase 2 RCT in hospitalized adults with severe COVID-19 in India (n = 464)</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged ≥18 years • Positive SARS-CoV-2 RT-PCR • PaO₂/FiO₂ = 200–300 mm Hg or respiratory rate >24 breaths/min with SpO₂ ≤93% on room air <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Critical illness <p>Interventions:</p> <ul style="list-style-type: none"> • 2 doses of 200 mL CP, transfused 24 hours apart • SOC <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Composite of progression to severe disease (defined as PaO₂/FiO₂ <100 mm Hg) any time within 28 days of enrollment or all-cause mortality at 28 days 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • CP (n = 235) and SOC (n = 229) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Median age was 52 years. • 75% of participants in the CP arm and 77% in the SOC arm were men. • Higher prevalence of diabetes in the CP arm (48%) than in SOC arm (38%). <p>Outcomes:</p> <ul style="list-style-type: none"> • No difference between the arms in the primary outcome of progression to severe disease or death (occurred in 18.7% of participants in CP arm and 17.9% in SOC arm). • A post hoc analysis evaluating outcomes among patients without detectable SARS-CoV-2 neutralizing antibody titers at baseline also revealed no benefit of CP. 	<p>Limitations:</p> <ul style="list-style-type: none"> • The study was not blinded. • SARS-CoV-2 antibody testing was not used to select donated CP units; therefore, many participants may have received CP units with low titers of SARS-CoV-2 neutralizing antibodies. <p>Interpretation:</p> <ul style="list-style-type: none"> • This trial did not demonstrate a benefit of CP in hospitalized patients with severe COVID-19.
Convalescent Plasma in COVID-19 Severe Pneumonia (PlasmAr Study)³			
<p>Double-blind, placebo-controlled, multicenter RCT in hospitalized adults with severe COVID-19 in Argentina (n = 333)</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged ≥18 years • Positive SARS-CoV-2 RT-PCR • Severe COVID-19 <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Critical illness <p>Interventions</p> <p><i>2:1 Randomization:</i></p> <ul style="list-style-type: none"> • Single dose (median volume 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • CP (n = 228) and placebo (n = 105) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Median age was 62 years. • 67.6% of the participants were men. • 64.9% of the participants had a coexisting condition at trial entry. • Median time from symptom onset to enrollment was 8 days. • Of 215 participants tested, 46% had no detectable SARS-CoV-2 antibodies at baseline. Median SARS-CoV-2 antibody titer in both the CP arm and placebo arm was 1:50. 	<p>Limitations:</p> <ul style="list-style-type: none"> • The majority of participants in both arms received concomitant glucocorticoid treatment, potentially masking subtle differences in clinical outcomes between the study arms.

Study Design	Methods	Results	Limitations and Interpretation
Convalescent Plasma in COVID-19 Severe Pneumonia (PlasmAr Study)³, continued			
	<p>500 mL) of CP pooled from 2–5 donors. Only plasma units with a SARS-CoV-2 viral spike-RBD IgG titer $\geq 1:800$ were transfused.</p> <ul style="list-style-type: none"> • Placebo <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Change in clinical status 30 days after intervention measured using a 6-point ordinal scale 	<p>Outcomes:</p> <ul style="list-style-type: none"> • No significant differences between the arms in the distribution of outcomes according to the categories on the 6-point ordinal scale (OR 0.83; 95% CI, 0.52–1.35). • 30-day mortality was similar in CP arm (11.0%) and placebo arm (11.4%). • Infusion-related AEs were more frequent in the CP arm than in the placebo arm (occurred in 4.8% vs. 1.9% of participants). 	<p>Interpretation:</p> <ul style="list-style-type: none"> • This trial did not demonstrate a benefit of CP in hospitalized patients with severe COVID-19.
Convalescent Plasma in Adults With Severe COVID-19⁴			
<p>Double-blind, Phase 2 RCT in hospitalized adults with severe COVID-19 (n = 223) in the United States (n = 73) and Brazil (n = 150)</p> <p><i>This is a preliminary report that has not yet been peer reviewed.</i></p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged ≥ 18 years • COVID-19 pneumonia • SpO₂ $\leq 94\%$ on room air or requirement for supplemental oxygen, IMV, or ECMO <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • >5 days on IMV or ECMO • Severe multiorgan failure <p>Interventions</p> <p><i>2:1 Randomization:</i></p> <ul style="list-style-type: none"> • Single dose of SARS-CoV-2 CP (approximately 250 mL). Only units with a SARS-CoV-2 viral spike-RBD IgG titer $\geq 1:400$ were transfused. • Non-SARS-CoV-2 plasma (normal control plasma) 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • CP (n = 150) and normal control plasma (n = 73) • Enrollment initiated in New York City in April 2020 and in Brazil in August 2020 <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Median age was 61 years. • 66% of the participants were men. • Median duration of symptoms prior to randomization was 9 days. • 57% of the participants required supplemental oxygen at baseline, 25% required high-flow oxygen or noninvasive ventilation, and 13% required IMV or ECMO. • There were some imbalances between the study arms at baseline. The CP arm included more women; the participants were younger and had slightly longer symptom durations. • 81% of the participants received corticosteroids. <p>Outcomes:</p> <ul style="list-style-type: none"> • No difference in clinical status on Day 28 was observed between the CP arm and the control arm (OR 1.5 for being in a better category with CP vs. control plasma; 95% CI, 0.83–2.68; <i>P</i> = 0.18). 	<p>Limitations:</p> <ul style="list-style-type: none"> • The intervention in the control group arm was blood plasma without SARS-CoV-2 antibodies. This ensured blinded administration; however, because the trial was not placebo controlled; it is not possible to identify potential harm due to plasma infusion. • Low sample size and number of events • There were imbalances in baseline characteristics between the study arms that may have impacted study outcomes. After adjustment for the imbalances, the

Study Design	Methods	Results	Limitations and Interpretation
Convalescent Plasma in Adults With Severe COVID-19⁴, continued			
	<p>Primary Endpoint:</p> <ul style="list-style-type: none"> Clinical status on Day 28, measured using an ordinal scale (initially with 7 categories, but modified to 6). <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> Time to clinical improvement In-hospital and 28-day mortality Time to discontinuation of supplemental oxygen Time to hospital discharge 	<ul style="list-style-type: none"> In-hospital mortality was lower in the CP arm (13%) than in the control arm (25%; HR 0.44; 95% CI, 0.22–0.91; $P = 0.034$). The treatment difference was not significant after adjustment for age, sex, and duration of symptoms at baseline. In both arms, mortality at 28 days was the same as in-hospital mortality. Time to oxygen discontinuation and time to hospital discharge were similar between the arms. 25.5% of patients in the CP arm vs. 36.1% in the control arm experienced SAEs. 	<p>difference in mortality between the arms was not significant.</p> <ul style="list-style-type: none"> The treatment difference in the primary outcome (clinical status on Day 28) was not statistically significant; mortality was a secondary outcome. There were no subgroup analyses for mortality. <p>Interpretation:</p> <ul style="list-style-type: none"> Although the difference between the CP arm and the non-SARS-CoV-2 antibody plasma arm for the primary outcome of clinical status on Day 28 was not statistically significant, the lower 28-day mortality in the CP arm suggests a potential benefit of CP in hospitalized patients with severe COVID-19.

Study Design	Methods	Results	Limitations and Interpretation
Early High-Titer Plasma Therapy to Prevent Severe COVID-19 in Older Adults⁵			
<p>Double-blind, placebo-controlled RCT in outpatients with mild COVID-19 in Argentina (n = 160)</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged >75 years or aged 65–74 years with ≥1 coexisting condition • Outpatient with <72 hours of mild COVID-19 symptoms <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Severe respiratory disease <p>Interventions:</p> <ul style="list-style-type: none"> • Single 250 mL dose of CP with an IgG titer against SARS-CoV-2 spike protein of >1:1000 • Placebo <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Severe respiratory disease defined as a respiratory rate ≥30 breaths/min and/or SpO₂ <93% on room air by Day 15 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • ITT analysis: CP (n = 80) and placebo (n = 80) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Mean age was 77 years. • Most of the patients had comorbidities. <p>Outcomes:</p> <ul style="list-style-type: none"> • 13 of 80 patients (16%) in the CP arm and 25 of 80 (31%) in the placebo arm experienced severe respiratory disease by Day 15 (relative risk 0.52; 95% CI, 0.29–0.94; P = 0.026). • 2 participants in the CP arm and 5 in the placebo arm died. • No solicited AEs were reported. 	<p>Limitations:</p> <ul style="list-style-type: none"> • The trial was terminated early because cases of COVID-19 at the study site decreased. • The trial included relatively few participants. <p>Interpretation:</p> <ul style="list-style-type: none"> • This trial demonstrated a benefit of CP in elderly outpatients with <72 hours of mild COVID-19 symptoms.
Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-Threatening COVID-19⁶			
<p>Multicenter, open-label, randomized trial in hospitalized adults with severe or life-threatening COVID-19 in China (n = 103)</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged ≥18 years • Positive SARS-CoV-2 PCR within 72 hours of randomization • Met study definition of severe or life-threatening COVID-19 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • CP (n = 52) and SOC (n = 51) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Median age was 70 years. • 58.3% of the participants were men. <p>Outcomes:</p> <ul style="list-style-type: none"> • No significant difference in time to clinical improvement between the CP arm and the control arm (HR 1.40; 95% CI, 0.79–2.49; P = 0.26). • No significant difference in mortality between the CP arm (16%) and the control arm (24%; P = 0.30). 	<p>Limitations:</p> <ul style="list-style-type: none"> • The study was not blinded. • The trial was stopped early because of decreasing numbers of cases of COVID-19 at the study site; therefore, the study lacked sufficient power to detect differences in clinical outcomes.

Study Design	Methods	Results	Limitations and Interpretation
Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-Threatening COVID-19⁶ , continued			
	<p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Baseline RBD-specific IgG antibody $\geq 1:64$ • Certain sequelae of severe COVID-19 (e.g., severe septic shock, severe heart failure) <p>Interventions:</p> <ul style="list-style-type: none"> • Single 4–13 mL/kg dose of CP. Only CP units with a SARS-CoV-2 viral spike-RBD-specific IgG titer of $\geq 1:640$ were transfused. • SOC <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Time to clinical improvement (patient discharge or a reduction of 2 points on a 6-point disease severity scale; 6 points = death, 1 point = hospital discharge) within 28 days. 		<ul style="list-style-type: none"> • Only 103 of 200 planned participants were randomized to receive treatment. • CP was administered late (approximately 1 month) into disease course. <p>Interpretation:</p> <ul style="list-style-type: none"> • This trial did not demonstrate a benefit of CP in hospitalized patients with severe or life-threatening COVID-19.
Early Versus Deferred Anti-SARS-CoV-2 Convalescent Plasma in Hospitalized Patients With COVID-19⁷			
<p>Open-label, single-center, Phase 2 randomized trial in hospitalized adults with COVID-19 in Chile (n = 58)</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged ≥ 18 years • ≤ 7 days of COVID-19 symptoms • High risk of progression to respiratory failure <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • PaO₂/FiO₂ <200 mm Hg • Mechanical ventilation 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • Immediate CP (n = 28) and deferred CP (n = 30) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Median age was 66 years. • 50% of the participants were men. • Median interval between symptom onset and randomization was 6 days. • 13 of 28 participants (43%) in the deferred CP arm received CP at a median of 3 days after enrollment. 	<p>Limitations:</p> <ul style="list-style-type: none"> • The study was not blinded. • Small sample size. <p>Interpretation:</p> <ul style="list-style-type: none"> • This trial did not demonstrate a benefit of immediate vs. deferred administration of CP in hospitalized COVID-19 patients with ≤ 7 days of COVID-19 symptoms.

Study Design	Methods	Results	Limitations and Interpretation
Early Versus Deferred Anti-SARS-CoV-2 Convalescent Plasma in Hospitalized Patients With COVID-19⁷, continued			
	<p>Interventions</p> <p><i>Immediate CP:</i></p> <ul style="list-style-type: none"> Two 400 mL doses of CP with anti-SARS-CoV-2 neutralizing antibody titers $\geq 1:400$, transfused 24 hours apart <p><i>Deferred CP:</i></p> <ul style="list-style-type: none"> CP transfusion only if PaO₂/FiO₂ <200 mm Hg, or if participant still required hospitalization for COVID-19 symptoms 7 days after enrollment <p>Primary Endpoint:</p> <ul style="list-style-type: none"> Composite of mechanical ventilation, hospitalization >14 days, or in-hospital death 	<p>Outcomes:</p> <ul style="list-style-type: none"> There was no difference between the arms in the percentage of participants who met the primary composite endpoint of death, mechanical ventilation, or >14 days hospitalization (32% in immediate CP arm vs. 33% in deferred CP arm; OR 0.95; 95% CI, 0.32–2.84). 18% of participants in the immediate CP arm vs. 7% in the deferred CP arm died within 30 days (OR 3.0; 95% CI, 0.5–17.2; <i>P</i> = 0.25). 	
Convalescent Plasma for COVID-19 (ConCOVID trial)⁸			
<p>Multicenter, open-label, RCT in hospitalized adults with COVID-19 in the Netherlands (n = 86)</p> <p><i>This is a preliminary report that has not yet been peer reviewed.</i></p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> Aged ≥ 18 years Clinical disease with positive SARS-CoV-2 RT-PCR within 96 hours of enrollment <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> Mechanical ventilation for >96 hours <p>Interventions:</p> <ul style="list-style-type: none"> One to two 300 mL doses of CP with anti-SARS-CoV-2 neutralizing antibody titers $\geq 1:80$ SOC 	<p>Number of Participants:</p> <ul style="list-style-type: none"> CP (n = 43) and SOC (n = 43) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> Median age was 63 years. Most of the participants were men. <p>Outcomes:</p> <ul style="list-style-type: none"> No differences in mortality (<i>P</i> = 0.95), length of hospital stay (<i>P</i> = 0.68), or disease severity at Day 15 (<i>P</i> = 0.58) were observed between the study arms. 	<p>Limitations:</p> <ul style="list-style-type: none"> The study was not blinded. Trial halted early by the investigators when the baseline SARS-CoV-2 neutralizing antibody titers of participant plasma and CP were found to be comparable, challenging the potential benefit of CP for the study population. Thus, the study lacked sufficient power to detect differences in clinical outcomes between the study arms.

Study Design	Methods	Results	Limitations and Interpretation
Convalescent Plasma for COVID-19 (ConCOVID trial)⁸, continued			
	<p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Day-60 mortality 		<ul style="list-style-type: none"> • Only 86 of 426 planned participants were randomized to receive CP or SOC. <p>Interpretation:</p> <ul style="list-style-type: none"> • This trial did not demonstrate a benefit of COVID-19 CP in hospitalized patients.
Convalescent Plasma for COVID-19 (ConPlas-19 Study)⁹			
<p>Multicenter, open-label, RCT in hospitalized adults with COVID-19 in Spain (n = 81)</p> <p><i>This is a preliminary report that has not yet been peer reviewed.</i></p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged ≥18 years <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Receiving IMV, noninvasive ventilation, or high-flow oxygen <p>Interventions:</p> <ul style="list-style-type: none"> • Single dose of 250–300 mL of CP plus SOC. • All administered units had neutralizing antibodies (VMNT-ID50: all titers >1:80, median titer 1:292, IQR 238–451; pseudovirus neutralizing ID50 assay: median titer 1:327; IQR 168–882) • SOC alone <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Proportion of patients in ordinal scale categories 5, 6, or 7 at Day 15. 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • CP (n = 38) and SOC (n = 43) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Mean age was 59 years. • At baseline, 49% of the participants were SARS-CoV-2 antibody positive. <p>Outcomes:</p> <ul style="list-style-type: none"> • 0 of 38 participants (0%) in the CP arm progressed to ordinal scale categories 5–7 vs. 6 of 43 participants (14.0%) in the SOC arm ($P = 0.57$, not statistically significant according to the planned analysis; but $P = 0.03$ using Fisher test as a post hoc sensitivity analysis given small numbers and the by-center heterogenous distribution). • 0 of 38 participants (0%) in the CP arm died vs. 4 of 43 (9.3%) in the SOC arm ($P = 0.06$). 	<p>Limitations:</p> <ul style="list-style-type: none"> • The study was not blinded. • The trial was stopped early because of decreasing numbers of COVID-19 cases at the study site and, thus, the study lacked sufficient power to detect differences in clinical outcomes. • Only 81 of planned 278 participants were enrolled. <p>Interpretation:</p> <ul style="list-style-type: none"> • Although the results did not reach statistical significance and only a small number of clinical events related to COVID-19 occurred, these results suggest a potential benefit of CP in hospitalized patients who are not receiving high-flow oxygen, noninvasive ventilation, or invasive ventilation.

Study Design	Methods	Results	Limitations and Interpretation
Clinical and Immunological Benefits of Convalescent Plasma Therapy in Severe COVID-19¹⁰			
<p>Single-center, open-label, RCT in hospitalized adults with COVID-19 and ARDS in India (n = 80)</p> <p><i>This is a preliminary report that has not yet been peer reviewed.</i></p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> Evidence of ARDS (defined as PaO₂/FiO₂ 100–300 mm Hg) Not on mechanical ventilation <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> Mechanical ventilation <p>Intervention:</p> <ul style="list-style-type: none"> 2 consecutive doses of ABO-matched 200 mL CP, 1 day apart SOC alone <p>Primary Endpoint:</p> <ul style="list-style-type: none"> All-cause mortality at Day 30 	<p>Number of Participants:</p> <ul style="list-style-type: none"> CP (n = 40) and SOC (n = 40) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> Mean age was 61 years. 71% of the participants were men. No difference in mean number of days of hospitalization at enrollment between the CP arm (4.2 days) and the SOC arm (3.9 days). <p>Outcomes:</p> <ul style="list-style-type: none"> 10 of 40 participants (25%) in the CP arm had died by Day 30 vs. 14 of 40 (35%) in the SOC arm. Difference in survival between the arms was not statistically significant (HR 0.6731; 95% CI, 0.3010–1.505). 	<p>Limitations:</p> <ul style="list-style-type: none"> The study was not blinded. The study lacked sufficient power to detect differences in clinical outcomes between the study arms. <p>Interpretation:</p> <ul style="list-style-type: none"> This trial did not demonstrate a benefit of CP in hospitalized patients with mild to moderate ARDS who are not receiving mechanical ventilation.
Convalescent Plasma Therapy Versus Standard Therapy in Patients With Severe COVID-19¹¹			
<p>Open-label, RCT in hospitalized adults with COVID-19 in Bahrain (n = 40)</p> <p><i>This is a preliminary report that has not yet been peer reviewed.</i></p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> Aged ≥21 years Radiologic evidence of pneumonia Requirement for oxygen therapy for COVID-19 <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> Requirement for IMV, noninvasive ventilation, or high-flow oxygen <p>Interventions:</p> <ul style="list-style-type: none"> Two 200 mL transfusions of CP over 24 hours SOC alone <p>Primary Endpoints:</p> <ul style="list-style-type: none"> Requirement for IMV or noninvasive ventilation 	<p>Number of Participants:</p> <ul style="list-style-type: none"> CP (n = 20) and SOC (n = 20) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> Mean age was 53 years in the CP arm and 51 years in the SOC arm. Most of the participants were men (75% in the CP arm and 85% in the SOC arm). <p>Outcomes:</p> <ul style="list-style-type: none"> 6 patients in the SOC arm and 4 patients in the CP arm required mechanical ventilation (risk ratio 0.67; 95% CI, 0.22–2.0; P = 0.72). 2 patients in the SOC arm died vs. 1 in the CP arm. 	<p>Limitations:</p> <ul style="list-style-type: none"> The study was not blinded. The study lacked sufficient power to detect differences in clinical outcomes between the study arms. <p>Interpretation:</p> <ul style="list-style-type: none"> This trial did not demonstrate a benefit of CP in hospitalized patients who are not receiving high-flow oxygen, noninvasive ventilation, or invasive ventilation.

Study Design	Methods	Results	Limitations and Interpretation
Convalescent Plasma Therapy Versus Standard Therapy in Patients With Severe COVID-19¹¹ , continued			
	<ul style="list-style-type: none"> In patients who require ventilation, duration of ventilation 		
Convalescent Plasma Antibody Levels and the Risk of Death from COVID-19¹²			
<p>Retrospective, indirect evaluation of a subset of patients from the Mayo Clinic COVID-19 CP EAP (n = 3,082). More than 100,000 patients hospitalized with COVID-19 in the United States received CP through the Mayo Clinic EAP.</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> Aged ≥18 years Severe or life-threatening (critical) COVID-19 Analysis limited to patients for whom samples were available for retrospective analysis of CP titer. <p>Intervention:</p> <ul style="list-style-type: none"> CP transfusion (no titer specified in real time; high, medium, and low titer CP determined retrospectively) <p>Primary Endpoint:</p> <ul style="list-style-type: none"> Mortality 30 days after CP transfusion 	<p>Number of Participants:</p> <ul style="list-style-type: none"> High-titer CP (n = 515), medium-titer CP (n = 2,006), and low-titer CP (n = 561) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> 61% of the participants were men. 48% of the participants were White and 37% were Hispanic/Latino. 61% of the participants required ICU-level care prior to infusion. 33% of the participants were on mechanical ventilation. 51% of the participants received corticosteroids; 31% received RDV. <p>Outcomes:</p> <ul style="list-style-type: none"> The analysis included 3,082 participants who received a single unit of CP. The participants were among 35,322 participants who had received CP through the EAP by July 4, 2020. Death within 30 days occurred in 115 of 515 patients (22%) in the high-titer group, 549 of 2,006 patients (27%) in the medium-titer group, and 166 of 561 patients (30%) in the low-titer group. Using a relative-risk regression model that assumed all patients who were discharged were alive at Day 30, patients in the high-titer group had a lower relative risk of death within 30 days than patients in the low-titer group (relative risk 0.82; 95% CI, 0.67–1.00). Among patients who received mechanical ventilation before transfusion, there was no difference in the risk of death between those who received high-titer CP and those who received low-titer CP (relative risk 1.02; 95% CI, 0.78–1.32). Mortality was lower among patients who were not receiving mechanical ventilation before transfusion (relative risk 0.66; 95% CI, 0.48–0.91). 	<p>Limitations:</p> <ul style="list-style-type: none"> Lack of untreated control arm limits interpretation of the safety and efficacy data; the possibility that differences in outcomes are attributable to harm from low-titer plasma rather than benefit from high-titer plasma cannot be excluded. Assays to determine the effective antibody titers remain limited, and the antibody titers of currently available CP from COVID-19 survivors are highly variable. Efficacy analysis relied on only a subset of EAP patients who represent a fraction of the patients who received CP through the EAP. Post hoc subgroups were selected by combining several subsetting rules that favored subgroups. This approach tends to overestimate the treatment effect. <p>Interpretation:</p> <ul style="list-style-type: none"> Given the lack of an untreated control arm and the limitations listed above, this retrospective analysis is not sufficient to establish the efficacy or safety of CP.

Key: AE = adverse event; ARDS = acute respiratory distress syndrome; ConCOVID Trial = Convalescent-plasma-for-COVID-9; ConPlas-19 Study = Convalescent Plasma for COVID-19; CP = convalescent plasma; EAP = Expanded Access Program; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; ID50 = 50% inhibitory dose; IgG = immunoglobulin G; IMV = invasive mechanical ventilation; ITT = intention to treat; the Panel = the COVID-19 Treatment Guidelines Panel; PaO₂/FiO₂ = ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; PCR = polymerase chain reaction; PLACID Trial = Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomized controlled trial; PlasmAr Study = A Randomized Trial of Convalescent Plasma in COVID-19 Severe Pneumonia; RBD = receptor binding domain; RCT = randomized controlled trial; RDV = remdesivir; RECOVERY = Randomised Evaluation of COVID-19 Therapy; RT-PCR = reverse transcriptase polymerase chain reaction; SAE = serious adverse event; SOC = standard of care; SpO₂ = saturation of oxygen; VMNT = virus microneutralization test

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Immunoglobulins: SARS-CoV-2 Specific

Last Updated: July 17, 2020

Recommendation

- There are insufficient data for the COVID-19 Treatment Guidelines Panel to recommend either for or against **severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunoglobulins** for the treatment of COVID-19.

Rationale

Currently, there are no clinical data on the use of SARS-CoV-2 immunoglobulins. Trials evaluating SARS-CoV-2 immunoglobulins are in development but not yet active and enrolling participants.

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

Concentrated antibody preparations derived from pooled plasma collected from individuals who have recovered from COVID-19 can be manufactured as SARS-CoV-2 immunoglobulin, which could potentially suppress the virus and modify the inflammatory response. The use of virus-specific immunoglobulins for other viral infections (e.g., cytomegalovirus [CMV] immunoglobulin for the prevention of post-transplant CMV infection and varicella zoster immunoglobulin for postexposure prophylaxis of varicella in individuals at high-risk) has proven to be safe and effective; however, there are currently no clinical data on the use of such products for COVID-19. Potential risks may include transfusion reactions. Theoretical risks may include antibody-dependent enhancement of infection.

Clinical Data

There are no clinical data on the use of SARS-CoV-2 immunoglobulins for the treatment of COVID-19. Similarly, there are no clinical data on use of specific immunoglobulin or hyperimmunoglobulin products in patients with severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS).

Considerations in Pregnancy

Pathogen-specific immunoglobulins are used clinically during pregnancy to prevent varicella zoster virus (VZV) and rabies and have also been used in clinical trials of therapies for congenital CMV infection.

Considerations in Children

Hyperimmunoglobulin has been used to treat several viral infections in children, including VZV, respiratory syncytial virus, and CMV; efficacy data on their use for other respiratory viruses is limited.

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

Last Updated: April 21, 2021

- The information in this table is derived from data on the use of these products in investigational trials in patients with COVID-19. The table includes dose recommendations from the FDA EUAs for patients with COVID-19 who meet specified criteria.
- There are limited or no data on dose modifications for patients with organ failure or those who require extracorporeal devices. Please refer to product labels, when available.
- There are currently not enough data to determine whether certain medications can be safely coadministered with therapies for the treatment of COVID-19. When using concomitant medications with similar toxicity profiles, consider performing additional safety monitoring.
- The potential additive, antagonistic, or synergistic effects and the safety of using combination therapies for the treatment of COVID-19 are unknown. Clinicians are encouraged to report AEs to the [FDA Medwatch program](#).
- For drug interaction information, please refer to product labels and visit the [Liverpool COVID-19 Drug Interactions website](#).
- For the Panel's recommendations for the drugs listed in this table, please refer to the drug-specific sections of the Guidelines and [Therapeutic Management of Adults With COVID-19](#).

Dosing Regimens	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Bamlanivimab Plus Etesevimab (Anti-SARS-CoV-2 Monoclonal Antibodies)				
Dose Recommended in EUA: <ul style="list-style-type: none"> • BAM 700 mg and ETE 1,400 mg IV administered together as a single dose 	<ul style="list-style-type: none"> • Nausea • Dizziness • Rash • Pruritis • Pyrexia • Hypersensitivity, including anaphylaxis and infusion-related reactions • Unexpected SAEs may occur. • These AEs were observed in a trial where the doses of BAM and ETE given (BAM 2,800 mg and ETE 2,800 mg) were higher than the EUA doses. 	<ul style="list-style-type: none"> • Only for administration in health care settings by qualified health care providers who have immediate access to medications to treat a severe infusion reaction and emergency medical services. • Monitor patient during the infusion and for ≥ 1 hour after the infusion is completed. 	<ul style="list-style-type: none"> • Drug-drug interactions are unlikely between BAM plus ETE and medications that are renally excreted or that are CYP substrates, inhibitors, or inducers. 	Availability: <ul style="list-style-type: none"> • BAM plus ETE is available through the FDA EUA for high-risk outpatients with mild to moderate COVID-19.¹ See Anti-SARS-CoV-2 Monoclonal Antibodies for a list of high-risk conditions. • A list of clinical trials is available: Bamlanivimab plus Etesevimab

Dosing Regimens	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Casirivimab Plus Imdevimab (Anti-SARS-CoV-2 Monoclonal Antibodies)				
<p>Dose Recommended in EUA:</p> <ul style="list-style-type: none"> • CAS 1,200 mg and IMD 1,200 mg IV administered together as a single dose 	<ul style="list-style-type: none"> • Hypersensitivity, including anaphylaxis and infusion-related reactions • Unexpected SAEs may occur. 	<ul style="list-style-type: none"> • Only for administration in health care settings by qualified health care providers who have immediate access to medications to treat a severe infusion reaction and emergency medical services. • Monitor patient during the infusion and for ≥ 1 hour after the infusion is completed. 	<ul style="list-style-type: none"> • Drug-drug interactions are unlikely between CAS plus IMD and medications that are renally excreted or that are CYP substrates, inhibitors, or inducers. 	<p>Availability:</p> <ul style="list-style-type: none"> • CAS plus IMD is available through the FDA EUA for high-risk outpatients with mild to moderate COVID-19.² See Anti-SARS-CoV-2 Monoclonal Antibodies for a list of high-risk conditions. • A list of clinical trials is available: Casirivimab plus Imdevimab
COVID-19 Convalescent Plasma				
<p>Dose Recommended in EUA Authorizing the Use of High-Titer COVID-19 CP for Hospitalized Patients With COVID-19:</p> <ul style="list-style-type: none"> • 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. 	<ul style="list-style-type: none"> • TRALI • TACO • Allergic reactions • Anaphylactic reactions • Febrile nonhemolytic reactions • Hemolytic reactions • Hypothermia • Metabolic complications • Transfusion-transmitted infections³ • Thrombotic events • Theoretical risk of antibody-mediated enhancement of infection and suppressed long-term immunity 	<ul style="list-style-type: none"> • Before administering CP to patients with a history of severe allergic or anaphylactic transfusion reactions, the Panel recommends consulting a transfusion medicine specialist who is associated with the hospital blood bank. • Monitor for transfusion-related reactions. • Monitor patient's vital signs at baseline and during and after transfusion. 	<ul style="list-style-type: none"> • Drug products should not be added to the IV infusion line for the blood product. 	<ul style="list-style-type: none"> • The decision to treat patients aged <18 years with COVID-19 CP should be based on an individualized assessment of risk and benefit.⁴ • Patients with impaired cardiac function and heart failure may require a smaller volume of CP or slower transfusion rate. <p>Availability:</p> <ul style="list-style-type: none"> • High-titer COVID-19 CP is available through the FDA EUA for hospitalized patients with COVID-19.⁵ See Anti-SARS-CoV-2 Monoclonal Antibodies. • A list of clinical trials is available: COVID-19 Convalescent Plasma

Dosing Regimens	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
SARS-CoV-2-Specific Immunoglobulin				
Dose varies by clinical trial	<ul style="list-style-type: none"> • TRALI • TACO • Allergic reactions • Antibody-mediated enhancement of infection • RBC alloimmunization • Transfusion-transmitted infections³ 	<ul style="list-style-type: none"> • Monitor for transfusion-related reactions. • Monitor patient's vital signs at baseline and during and after transfusion. 	<ul style="list-style-type: none"> • Drug products should not be added to the IV infusion line for the blood product. 	<ul style="list-style-type: none"> • A list of clinical trials is available: SARS-CoV-2 Immunoglobulin

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

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

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Mesenchymal Stem Cells

Mesenchymal stem cells are investigational products that have been studied extensively for broad clinical applications in regenerative medicine¹ 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 (**AI**).

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](https://www.clinicaltrials.gov) for a list of clinical trials evaluating mesenchymal stem cells for the treatment of COVID-19, COVID-19-related ARDS, and COVID-19-associated multisystem inflammatory syndrome in children (MIS-C).

Adverse Effects

Risks associated with mesenchymal stem cell transfusion appear to be uncommon. The potential risks include the potential for mesenchymal stem cells to multiply or change into inappropriate cell types, product contamination, growth of tumors, infections, thrombus formation, and administration site reactions.¹¹

Considerations in Pregnancy

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

Considerations in Children

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

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Immunomodulators Under Evaluation for the Treatment of COVID-19

Last Updated: April 21, 2021

Summary Recommendations

See [Therapeutic Management of Adults with COVID-19](#) for the COVID-19 Treatment Guidelines Panel's (the Panel's) recommendations on the use of the following:

- Baricitinib in combination with remdesivir when corticosteroids cannot be used,
- Dexamethasone (or other corticosteroids) with or without remdesivir, *and*
- Tocilizumab with dexamethasone (with or without remdesivir).

See additional recommendations on the use of baricitinib and tocilizumab below.

Other Immunomodulators

There are insufficient data for the Panel to recommend either for or against the use of the following immunomodulators for the treatment of COVID-19:

- Baricitinib in combination with a corticosteroid; because both agents are potent immunosuppressants, there is a potential additive risk of infection.
- Baricitinib in combination with remdesivir for hospitalized patients with COVID-19 when corticosteroids can be used
- Colchicine for nonhospitalized patients with COVID-19
- Fluvoxamine
- Interleukin (IL)-1 inhibitors (e.g., anakinra)
- Interferon beta for the treatment of early (i.e., <7 days from symptom onset) mild to moderate COVID-19
- Sarilumab for patients who are within 24 hours of admission to the intensive care unit (ICU) and who require invasive mechanical ventilation, noninvasive ventilation, or high-flow oxygen (>0.4 FiO₂/30 L/min of oxygen flow)
- Tocilizumab for most hospitalized patients with hypoxemia who require conventional oxygen therapy (see [Therapeutic Management of Adults With COVID-19](#) for more detailed information)

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

- **Baricitinib** without **remdesivir (AIII)**
- **Colchicine** for hospitalized patients with COVID-19 (**AIII**)
- **Interferons (alfa or beta)** for the treatment of severely or critically ill patients with COVID-19 (**AIII**)
- Kinase inhibitors:
 - Bruton's tyrosine kinase inhibitors (e.g., **acalabrutinib, ibrutinib, zanubrutinib**) (**AIII**)
 - Janus kinase inhibitors other than baricitinib (e.g., **ruxolitinib, tofacitinib**) (**AIII**)
- **Non-SARS-CoV-2-specific intravenous immunoglobulin (IVIG) (AIII)**. This recommendation should not preclude the use of IVIG when it is otherwise indicated for the treatment of complications that arise during the course of COVID-19.
- **Sarilumab** for patients who do not require ICU-level care or who are admitted to the ICU for >24 hours but do not require invasive mechanical ventilation, noninvasive ventilation, or supplemental oxygen administered through a high-flow device (**BIIa**)
- The anti-IL-6 monoclonal antibody **siltuximab (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

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 studied for the prevention of major cardiovascular events in those with coronary artery disease.² Colchicine has several potential mechanisms of action, including mechanisms that reduce the chemotaxis of neutrophils, inhibit inflammasome signaling, and decrease the production of cytokines such as interleukin-1 beta.³ When colchicine is administered early in the course of COVID-19, these mechanisms may potentially mitigate or prevent inflammation-associated manifestations of the disease. These anti-inflammatory properties (as well as the drug's limited immunosuppressive potential, widespread availability, and favorable safety profile) have prompted investigation of colchicine for the treatment of COVID-19.

Recommendations

- There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of colchicine for the treatment of nonhospitalized patients with COVID-19.
- A large, randomized trial in outpatients, the Colchicine Coronavirus SARS-CoV-2 Trial (COLCORONA), did not reach its primary efficacy endpoint of reducing hospitalizations and death. However, a slight reduction in hospitalizations was observed in the subset of patients whose diagnosis was confirmed by a positive nasopharyngeal swab on a SARS-CoV-2 polymerase chain reaction (PCR) test.
- The Panel **recommends against** the use of colchicine in hospitalized patients for the treatment of COVID-19, except in a clinical trial (**AIII**).

Clinical Data for COVID-19

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

COLCORONA was a contactless, double-blind, placebo-controlled randomized trial in outpatients who were diagnosed with COVID-19 within 24 hours of enrollment.⁴ Participants had to have at least one risk factor for COVID-19 complications, including age ≥ 70 years, body mass index ≥ 30 , diabetes mellitus, uncontrolled hypertension, known respiratory disease, heart failure or coronary disease, fever $\geq 38.4^\circ\text{C}$ within the last 48 hours, dyspnea at presentation, bicytopenia, pancytopenia, or the combination of high neutrophil count and low lymphocyte count. Participants were randomized 1:1 to receive colchicine 0.5 mg twice daily for 3 days and then once daily for 27 days or placebo. The primary endpoint was a composite of death or hospitalization by Day 30; secondary endpoints included components of the primary endpoint, as well as the need for mechanical ventilation by Day 30. Given the contactless design of the study, outcomes were ascertained by patient self-report via telephone at 15 and 30 days after randomization; in some cases, clinical data was confirmed by medical chart review.

Results

- The study enrolled a total of 4,488 participants.
- The primary endpoint was reached in 104 of 2,235 participants (4.7%) in the colchicine arm versus in 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 a nasopharyngeal PCR test (93% of those enrolled), those in the colchicine arm were significantly 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 who were SARS-CoV-2 positive, there were fewer hospitalizations (a secondary outcome) in the colchicine arm (4.5% of patients) than in the placebo arm (5.9% of patients; OR 0.75; 95% CI, 0.57–0.99).
- More gastrointestinal adverse events occurred in the colchicine arm, including diarrhea (occurred in 13.7% of patients vs. in 7.3% of patients in the placebo arm; $P < 0.001$). Unexpectedly, more pulmonary emboli were reported among patients in the colchicine arm (11 events [0.5% of patients] vs. 2 [0.1% of patients] in the placebo arm; $P = 0.01$).

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.
- Patient-reported clinical outcomes were potentially misclassified.

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

This study has not been published.

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

Results

- In a preliminary, unpublished report of results for 11,162 patients randomized to colchicine or usual care, there was no significant difference in the primary endpoint of 28-day mortality between the arms.
- Of the 2,178 patients who died, 20% were in the colchicine arm versus 19% in the usual care arm (risk ratio 1.02; 95% CI, 0.94–1.11; $P = 0.63$).
- Among the patients who died, 94% had received concomitant corticosteroids.

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

The GRreek Study in the Effects of Colchicine in Covid-19 cOmplications Prevention (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 up to 3 weeks) or standard of care alone.⁶

Results

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

(occurred in 45.5% vs. 18.0% of participants in the colchicine and standard of care arms, respectively; $P = 0.003$).

Limitations

- The number of clinical events reported for the trial was small.
- The study design was open-label treatment assignment.

The results of several small randomized trials and retrospective cohort studies that have evaluated various doses and durations of colchicine in hospitalized patients with COVID-19 have been published in peer-reviewed journals or made available as preliminary, non-peer-reviewed reports.⁷⁻¹⁰ Some have shown benefits of colchicine use, including less need for supplemental oxygen, improvements in clinical status on an ordinal clinical scale, and reductions in certain inflammatory markers. In addition, some studies have reported higher discharge rates or fewer deaths among patients who received colchicine than among those who received comparator drugs or placebo. However, these studies also had significant design or methodological limitations, including small sample sizes, open-label designs, and differences between the treatment arms in participants' clinical and demographic characteristics and the permitted use of various cotreatments (e.g., remdesivir, corticosteroids), that limit interpretability of the studies.

Adverse Effects, Monitoring, and Drug-Drug Interactions

Common side effects of colchicine include diarrhea, nausea, vomiting, cramping, abdominal 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, such as atorvastatin, lovastatin, and simvastatin, due to potential competitive interactions mediated by CYP3A4 and P-gp pathways.^{11,12} Fatal colchicine toxicity has been reported in individuals with renal or hepatic impairment who received colchicine in conjunction with P-gp inhibitors or strong CYP3A4 inhibitors.

Considerations in Pregnancy

There are limited data on the use of colchicine in pregnancy. Fetal risk cannot be ruled out based on data from animal studies and the drug's mechanism of action. Colchicine crosses the placenta and has antimetabolic properties, which raises a theoretical concern for teratogenicity. However, a recent systematic review of the literature did not find higher rates of miscarriage or major fetal malformations in pregnant women who were exposed to colchicine than in pregnant women who were not exposed to the drug. There are no data for colchicine use in pregnant women with acute COVID-19. Risks of use should be balanced against potential benefits.^{11,13}

Considerations in Children

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

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Corticosteroids

Last Updated: November 3, 2020

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

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

Rationale for Use of Corticosteroids in Patients With COVID-19

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

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

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

Corticosteroids used in various formulations and doses and for varying durations in patients with COVID-19 were also studied in several smaller randomized controlled trials.¹⁶⁻²⁰ Some of these trials were stopped early due to under enrollment following the release of the results from the RECOVERY trial. Given that the sample size of many these trials was insufficient to assess efficacy, evidence to support the use of methylprednisolone and hydrocortisone for the treatment of COVID-19 is not as robust as that demonstrated for dexamethasone in the RECOVERY trial. Data from some of these studies can be found in [Table 4a](#).

Corticosteroids Other Than Dexamethasone

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

Monitoring, Adverse Effects, and Drug-Drug Interactions

- Clinicians should closely monitor patients with COVID-19 who are receiving dexamethasone for adverse effects (e.g., hyperglycemia, secondary infections, psychiatric effects, avascular necrosis).
- Prolonged use of systemic corticosteroids may increase the risk of reactivation of latent infections (e.g., hepatitis B virus [HBV], herpesvirus infections, strongyloidiasis, tuberculosis).
- The risk of reactivation of latent infections for a 10-day course of dexamethasone (6 mg once daily) is not well-defined. When initiating dexamethasone, appropriate screening and treatment to reduce the risk of *Strongyloides* hyperinfection in patients at high risk of strongyloidiasis (e.g., patients from tropical, subtropical, or warm, temperate regions or those engaged in agricultural activities)²²⁻²⁴ or fulminant reactivations of HBV²⁵ should be considered.
- Dexamethasone is a moderate cytochrome P450 (CYP) 3A4 inducer. As such, it may reduce the concentration and potential efficacy of concomitant medications that are CYP3A4 substrates. Clinicians should review a patient's medication regimen to assess potential interactions.
- Coadministration of remdesivir and dexamethasone has not been formally studied, but a clinically significant pharmacokinetic interaction is not predicted.
- Dexamethasone should be continued for up to 10 days or until hospital discharge, whichever comes first.

Considerations in Pregnancy

A short course of betamethasone and dexamethasone, which are known to cross the placenta, is routinely used to decrease neonatal complications of prematurity in women with threatened preterm delivery.^{26,27}

Given the potential benefit of decreased maternal mortality and the low risk of fetal adverse effects for a short course of dexamethasone therapy, the Panel recommends using **dexamethasone** in hospitalized

pregnant women with COVID-19 who are mechanically ventilated (**AIII**) or who require supplemental oxygen but who are not mechanically ventilated (**BIII**).

Considerations in Children

The safety and effectiveness of dexamethasone or other corticosteroids for COVID-19 treatment have not been sufficiently evaluated in pediatric patients. Importantly, the RECOVERY trial did not include a significant number of pediatric patients, and mortality from COVID-19 is significantly lower among pediatric patients than among adult patients. Thus, caution is warranted when extrapolating the results of the RECOVERY trial to patients aged <18 years. Dexamethasone may be beneficial in pediatric patients with COVID-19 respiratory disease who require mechanical ventilation. Use of dexamethasone in patients who require other forms of supplemental oxygen support should be considered on a case-by-case basis and is generally not recommended for pediatric patients who require only low levels of oxygen support (i.e., nasal cannula only). Additional studies are needed to evaluate the use of steroids for the treatment of COVID-19 in pediatric patients, including for multisystem inflammatory syndrome in children (MIS-C).

Clinical Trials

Several clinical trials to evaluate corticosteroids for the treatment of COVID-19 are currently underway or in development. Please see [ClinicalTrials.gov](https://www.clinicaltrials.gov) for the latest information.

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Table 4a. Corticosteroids: Selected Clinical Data

Last Updated: February 11, 2021

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

Study Design	Methods	Results	Limitations and Interpretation
Dexamethasone in Hospitalized Patients With COVID-19—Preliminary Report (RECOVERY Trial)¹			
<p>Multi-center, randomized open-label adaptive trial in hospitalized patients with suspected or confirmed COVID-19 (n = 6,425)</p> <p>Country: United Kingdom</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> Hospitalization with clinically suspected or laboratory-confirmed SARS-CoV-2 infection <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> Physician determination that risks of participation too great based on patient's medical history or an indication for corticosteroid therapy outside of the study <p>Interventions:</p> <ul style="list-style-type: none"> Patients randomized 2:1 to receive: <ul style="list-style-type: none"> Dexamethasone 6 mg PO or IV once daily plus SOC for up to 10 days or until hospital discharge, whichever came first, <i>or</i> SOC alone <p>Primary Endpoint:</p> <ul style="list-style-type: none"> All-cause mortality at 28 days after randomization 	<p>Number of Participants:</p> <ul style="list-style-type: none"> Dexamethasone plus SOC (n = 4,321) and SOC (n = 2,104) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> Mean age was 66 years. 64% of participants were men. 56% of participants had ≥ 1 comorbidity; 24% had diabetes. 89% of participants had laboratory-confirmed SARS-CoV-2 infection. At randomization, 16% of participants received invasive mechanical ventilation or ECMO, 60% required supplemental oxygen but not invasive ventilation, and 24% required no oxygen supplementation. 0% to 3% of the participants in both arms received RDV, HCQ, LPV/RTV, or tocilizumab; approximately 8% of participants in SOC alone arm received dexamethasone after randomization. <p>Outcomes:</p> <ul style="list-style-type: none"> 28-day mortality was 22.9% in dexamethasone arm and 25.7% in SOC arm (age-adjusted rate ratio 0.83; 95% CI, 0.75–0.93; $P < 0.001$). 	<p>Limitations:</p> <ul style="list-style-type: none"> Open label study This preliminary study analysis did not include the results for key secondary endpoints (e.g., cause-specific mortality, need for renal replacement), AEs, and the efficacy of dexamethasone in key subgroups (e.g., patients with comorbidities). Study participants with COVID-19 who required oxygen (but not mechanical ventilation) had variable disease severity; it is unclear whether all patients in this heterogeneous group derived benefit from dexamethasone, or whether benefit is restricted to those requiring higher levels of supplemental oxygen or oxygen delivered through a high-flow device. The age distribution of participants differed by respiratory status at randomization. The survival benefit of dexamethasone for mechanically ventilated patients aged >80 years is unknown because only 1% of the participants in this group were ventilated.

Study Design	Methods	Results	Limitations and Interpretation
Dexamethasone in Hospitalized Patients With COVID-19—Preliminary Report (RECOVERY Trial)¹, continued			
		<ul style="list-style-type: none"> The treatment effect of dexamethasone varied by baseline severity of COVID-19. Survival benefit appeared greatest among participants who required invasive mechanical ventilation at randomization. Among these participants, 28-day mortality was 29.3% in dexamethasone arm vs. 41.4% in SOC arm (rate ratio 0.64; 95% CI, 0.51–0.81). Among patients who required supplemental oxygen but not mechanical ventilation at randomization, 28-day mortality was 23.3% in dexamethasone arm vs. 26.2% in SOC arm (rate ratio 0.82; 95% CI, 0.72–0.94). No survival benefit in participants who did not require oxygen therapy at enrollment. Among these participants, 28-day mortality was 17.8% in dexamethasone arm vs. 14.0% in SOC arm (rate ratio 1.19; 95% CI, 0.91–1.55). 	<ul style="list-style-type: none"> It is unclear whether younger patients were more likely to receive mechanical ventilation than patients aged >80 years, given similar disease severity at baseline, with older patients preferentially assigned to oxygen therapy. The high baseline mortality of this patient population may limit generalizability of the study results to populations with a lower baseline mortality. <p>Interpretation:</p> <ul style="list-style-type: none"> In hospitalized patients with severe COVID-19 who required oxygen support, using dexamethasone 6 mg daily for up to 10 days reduced mortality at 28 days, with the greatest benefit seen in those who were mechanically ventilated at baseline. There was no observed survival benefit of dexamethasone in patients who did not require oxygen support at baseline.
Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-Analysis (REACT Working Group)²			
<p>Meta-analysis of 7 RCTs of corticosteroids in critically ill patients with COVID-19 (n = 1,703)</p> <p>Countries: Multinational</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> RCTs evaluating corticosteroids in critically ill patients with COVID-19 (identified via comprehensive search of ClinicalTrials.gov, Chinese Clinical Trial Registry, and EU Clinical Trials Register) 	<p>Number of Participants:</p> <ul style="list-style-type: none"> Corticosteroids (n = 678) and usual care or placebo (n = 1,025) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> Median age was 60 years. 29% of patients were women. 1,559 patients (91.5%) were on mechanical ventilation. 	<p>Limitations:</p> <ul style="list-style-type: none"> The design of the trials included in the meta-analysis differed in several ways, including the following: <ul style="list-style-type: none"> Definition of critical illness Specific corticosteroid used Dose of corticosteroid Duration of corticosteroid treatment

Study Design	Methods	Results	Limitations and Interpretation
Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-Analysis (REACT Working Group)², continued			
	<p>Interventions:</p> <ul style="list-style-type: none"> • Corticosteroids (i.e., dexamethasone, hydrocortisone, methylprednisolone) • Usual care or placebo <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • All-cause mortality up to 30 days after randomization 	<ul style="list-style-type: none"> • 47% of patients were on vasoactive agents at randomization across the 6 trials that reported this information. <p>Outcomes:</p> <ul style="list-style-type: none"> • Mortality was assessed at 28 days in 5 trials, 21 days in 1 trial, and 30 days in 1 trial. • Reported all-cause mortality at 28 days: Death occurred in 222 of 678 patients (32.7%) in corticosteroids group vs. 425 of 1,025 patients (41.5%) in usual care or placebo group; summary OR 0.66 (95% CI, 0.53–0.82; $P < 0.001$). • The fixed-effect summary ORs for the association with all-cause mortality were: <ul style="list-style-type: none"> • Dexamethasone: OR 0.64 (95% CI, 0.50–0.82; $P < 0.001$) in 3 trials with 1,282 patients • Hydrocortisone: OR 0.69 (95% CI, 0.43–1.12; $P = 0.13$) in 3 trials with 374 patients. • Methylprednisolone: OR 0.91 (95% CI, 0.29–2.87; $P = 0.87$) in 1 trial with 47 patients • For patients on mechanical ventilation ($n = 1,559$): OR 0.69 (95% CI, 0.55–0.86), with mortality of 30% for corticosteroids vs. 38% for usual care or placebo • For patients not on mechanical ventilation ($n = 144$): OR 0.41 (95% CI, 0.19–0.88) with mortality of 23% for corticosteroids vs. 42% for usual care or placebo • Across the 6 trials that reported SAEs, 18.1% of patients randomized to corticosteroids and 23.4% randomized to usual care or placebo experienced SAEs. 	<ul style="list-style-type: none"> • Type of control group (i.e., usual care or placebo) • Reporting of SAEs • The RECOVERY trial accounted for 59% of the participants, and 3 trials enrolled <50 patients each. • Some studies confirmed SARS-CoV-2 infection for participant inclusion while others enrolled participants with either probable or confirmed infection. • Although the risk of bias was low in 6 of the 7 trials, it was assessed as “some concerns” for 1 trial (which contributed only 47 patients). <p>Interpretation:</p> <ul style="list-style-type: none"> • Systemic corticosteroids decrease 28-day mortality in critically ill patients with COVID-19 without safety concerns. • Most of the participants were from the RECOVERY trial, thus the evidence of benefit in the meta-analysis is strongest for dexamethasone, the corticosteroid used in the RECOVERY trial.

Study Design	Methods	Results	Limitations and Interpretation
Methylprednisolone as Adjunctive Therapy for Patients Hospitalized With COVID-19 (Metcovid): A Randomised, Double-Blind, Phase IIb, Placebo-Controlled Trial³			
<p>Randomized, double-blind, placebo-controlled, single-center study of short-course methylprednisolone in hospitalized patients with confirmed or suspected COVID-19 pneumonia (n = 416)</p> <p>Country: Brazil</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged ≥18 years • Suspected or confirmed COVID-19 • SpO₂ ≤94% on room air <i>or</i> while using supplementary oxygen <i>or</i> under invasive mechanical ventilation <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Hypersensitivity to methylprednisolone • Chronic use of corticosteroids or immunosuppressive agents • HIV, decompensated cirrhosis, chronic renal failure <p>Interventions:</p> <ul style="list-style-type: none"> • Methylprednisolone IV 0.5 mg/kg twice daily for 5 days • Placebo (saline) IV <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Mortality by Day 28 <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> • Early mortality at Days 7 and 14 • Need for mechanical ventilation by Day 7 • Need for insulin by Day 28 • Positive blood culture at Day 7, sepsis by Day 28 • Mortality by Day 28 in specified subgroups 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • mITT analysis (n = 393): Methylprednisolone (n = 194) and placebo (n = 199) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Mean age was 55 years. • 65% of patients were men. • 29% of patients had diabetes. • At enrollment, 34% of participants in each group required invasive mechanical ventilation; 51% in methylprednisolone group and 45% in placebo group required supplemental oxygen. • Median time from illness onset to randomization was 13 days (IQR 9–16). • None of the participants received anti-IL-6, anti-IL-1, RDV, or convalescent plasma. • Hydrocortisone use for shock among patients was 8.7% in methylprednisolone group and 7.0% in placebo group. <p>Primary Outcomes:</p> <ul style="list-style-type: none"> • No difference in 28-day mortality: 37.1% in methylprednisolone arm vs. 38.2% in placebo arm (HR 0.92; 95% CI, 0.67–1.28; <i>P</i> = 0.63). <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> • No difference between groups in early mortality at Day 7 (HR 0.68; 95% CI, 0.43–1.06) or Day 14 (HR 0.82; 95% CI, 0.57–1.18) • No difference in need for mechanical ventilation by Day 7: 19.4% of methylprednisolone recipients vs. 16.8% of placebo recipients (<i>P</i> = 0.65) 	<p>Limitations:</p> <ul style="list-style-type: none"> • The median days from illness onset to randomization was longer than in other corticosteroid studies. • The high baseline mortality of this patient population may limit generalizability of the study results to populations with a lower baseline mortality. <p>Interpretation:</p> <ul style="list-style-type: none"> • Use of weight-based methylprednisolone for 5 days did not reduce overall 28-day mortality. • In a post hoc subgroup analysis, mortality among those aged >60 years was lower in the methylprednisolone group than in the placebo group.

Study Design	Methods	Results	Limitations and Interpretation
Methylprednisolone as Adjunctive Therapy for Patients Hospitalized With COVID-19 (Metcovid): A Randomised, Double-Blind, Phase IIb, Placebo-Controlled Trial³, continued			
		<ul style="list-style-type: none"> • No significant difference between the methylprednisolone and placebo groups in need for insulin (59.5% vs. 49.4% of patients), positive blood cultures at Day 7 (8.3% vs. 8.0% of patients), or sepsis by Day 28 (38.1% vs. 38.7% of patients) • In post hoc analysis, 28-day mortality in participants aged >60 years was lower in methylprednisolone group than in placebo group (46.6% vs. 61.9%; HR 0.63; 95% CI, 0.41–0.98). 	
Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial⁴			
<p>Multicenter, randomized, clinical trial in patients with COVID-19 and moderate to severe ARDS (n = 299) Country: Brazil</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged ≥18 years • Confirmed or suspected COVID-19 • On mechanical ventilation within 48 hours of meeting criteria for moderate to severe ARDS with PaO₂/FiO₂ ≤200 mm Hg <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Recent corticosteroid use • Use of immunosuppressive drugs in the past 21 days • Expected death in next 24 hours <p>Interventions:</p> <ul style="list-style-type: none"> • Dexamethasone 20 mg IV daily for 5 days, then 10 mg IV daily for 5 days or until ICU discharge plus SOC • SOC alone 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • ITT analysis (n = 299): Dexamethasone plus SOC (n = 151) and SOC alone (n = 148) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Dexamethasone group included more women than the SOC group (40% vs. 35%), more patients with obesity (31% vs. 24%), and fewer patients with diabetes (38% vs. 47%). • Other baseline characteristics were similar for the dexamethasone and SOC groups: <ul style="list-style-type: none"> • Mean age was 60 vs. 63 years; vasopressor use by 66% vs. 68% of patients; mean PaO₂/FiO₂ of 131 mm Hg vs. 133 mm Hg. • Median time from symptom onset to randomization was 9–10 days. • Median time from mechanical ventilation to randomization was 1 day. • No patients received RDV; anti-IL-6 and convalescent plasma were not widely available. • Median duration of dexamethasone therapy was 10 days (IQR 6–10 days). 	<p>Limitations:</p> <ul style="list-style-type: none"> • Open-label study • The study was underpowered to assess some outcomes because it stopped enrollment after data from the RECOVERY trial were released. • During the study, 35% of the patients in the SOC group received corticosteroids for shock, bronchospasm, or other reasons. • Patients who were discharged from the hospital before 28 days were not followed for rehospitalization or mortality. • The high baseline mortality of the patient population may limit generalizability of the study results to populations with a lower baseline mortality. <p>Interpretation:</p> <ul style="list-style-type: none"> • Compared with SOC alone, dexamethasone at a higher dose than used in the RECOVERY trial plus SOC

Study Design	Methods	Results	Limitations and Interpretation
Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial⁴, continued			
	<p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Mean number of days alive and free from mechanical ventilation by Day 28 <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> • All-cause mortality at Day 28 • ICU-free days by Day 28 • Duration of mechanical ventilation by Day 28 • Score on 6-point WHO ordinal scale at Day 15 • SOFA score at 7 days • Components of the primary outcome or in the outcome of discharged alive within 28 days 	<ul style="list-style-type: none"> • 35% of patients in SOC alone group also received corticosteroids. <p>Primary Outcomes:</p> <ul style="list-style-type: none"> • The mean number of days alive and free from mechanical ventilation by Day 28 was higher in the dexamethasone group than in the SOC group (6.6 vs. 4.0 days, estimated difference of 2.3 days; 95% CI, 0.2–4.4; $P = 0.04$). <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> • There were no differences between the dexamethasone and SOC groups for the following outcomes: <ul style="list-style-type: none"> • All-cause mortality at Day 28 (56.3% vs. 61.5%; HR 0.97; 95% CI, 0.72–1.31; $P = 0.85$) • ICU-free days by Day 28 (mean of 2.1 vs. 2.0 days; $P = 0.50$) • Duration of mechanical ventilation by Day 28 (mean of 12.5 vs. 13.9 days; $P = 0.11$) • Score on 6-point WHO ordinal scale at Day 15 (median score of 5 for both groups) • The mean SOFA score at 7 days was lower in the dexamethasone group than in the SOC group (6.1 vs. 7.5, difference -1.16; 95% CI, -1.94 to -0.38; $P = 0.004$). • The following safety outcomes were comparable for dexamethasone and SOC groups: need for insulin (31.1% vs. 28.4%), new infections (21.9% vs. 29.1%), bacteremia (7.9% vs. 9.5%), and other SAEs (3.3% vs. 6.1%). • In post hoc analysis, the dexamethasone group had a lower cumulative probability of death or mechanical ventilation at Day 15 than the SOC group (67.5% vs. 80.4%; OR 0.46; 95% CI, 0.26–0.81; $P = 0.01$). 	<p>increased the number of days alive and free of mechanical ventilation over 28 days of follow-up in patients with COVID-19 and moderate to severe ARDS.</p> <ul style="list-style-type: none"> • Dexamethasone was not associated with an increased risk of AEs in this population. • More than one-third of those randomized to the standard care alone group also received corticosteroids; it is impossible to determine the effect of corticosteroid use in these patients on the overall study outcomes.

Study Design	Methods	Results	Limitations and Interpretation
Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19: A Randomized Clinical Trial⁵			
<p>Multicenter, randomized, double-blind, sequential trial in patients with confirmed or suspected COVID-19 and acute respiratory failure (n = 149)</p> <p>Country: France</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged ≥18 years • Confirmed SARS-CoV-2 infection or radiographically suspected COVID-19, with at least 1 of 4 severity criteria: <ul style="list-style-type: none"> • Need for mechanical ventilation with PEEP ≥5 cm H₂O • High-flow oxygen with PaO₂/FiO₂ <300 mm Hg and FiO₂ ≥50% • Reservoir mask oxygen with PaO₂/FiO₂ <300 mm Hg (estimated) • Pneumonia severity index >130 (scoring table) <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Septic shock • Do-not-intubate orders <p>Interventions:</p> <ul style="list-style-type: none"> • Continuous infusion hydrocortisone 200 mg/day until Day 7, then hydrocortisone 100 mg/day for 4 days, and then hydrocortisone 50 mg/day for 3 days, for a total treatment duration of 14 days • Patients who showed clinical improvement by Day 4 were switched to a shorter 8-day regimen. 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • ITT analysis (n = 149 participants): Hydrocortisone (n = 76) and placebo (n = 73) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Mean age of participants was 62 years; 70% were men; median BMI was 28. • 96% of participants had confirmed SARS-CoV-2 infection. • Median symptom duration before randomization was 9 days in hydrocortisone group vs. 10 days in placebo group. • 81% of the patients overall were mechanically ventilated, and 24% in hydrocortisone group and 18% in placebo group were receiving vasopressors. • Among the patients receiving concomitant COVID-19 treatment, 3% received RDV, 14% LPV/RTV, 13% HCQ, and 34% HCQ plus AZM. • Median treatment duration was 10.5 days in hydrocortisone group vs. 12.8 days in placebo group (P = 0.25). <p>Primary Outcome:</p> <ul style="list-style-type: none"> • There was no difference in the proportion of patients with treatment failure by Day 21, which occurred in 32 of 76 patients (42.1%) in hydrocortisone group and 37 of 73 patients (50.7%) in placebo group (difference -8.6%; 95% CI, -24.9% to 7.7%; P = 0.29). <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> • There was no difference between the groups in the need for intubation, rescue strategies, or oxygenation (i.e., change in PaO₂/FiO₂). • Among the patients who did not require mechanical ventilation at baseline, 8 of 16 patients (50%) in hydrocortisone group required subsequent 	<p>Limitations:</p> <ul style="list-style-type: none"> • Small sample size. Planned sample size of 290, but 149 enrolled because study was terminated early after the release of results from the RECOVERY trial. • Limited information about comorbidities (e.g., hypertension) • Participants' race and/or ethnicity were not reported. • Nosocomial infections were recorded but not adjudicated. <p>Interpretation:</p> <ul style="list-style-type: none"> • Compared to placebo, hydrocortisone did not reduce treatment failure (defined as death or persistent respiratory support) at Day 21 in ICU patients with COVID-19 and acute respiratory failure. • Because this study was terminated early, it is difficult to make conclusions about the efficacy and safety of hydrocortisone therapy. • The starting dose of hydrocortisone used in this study were slightly higher than the 6 mg dose of dexamethasone used in the RECOVERY study. The hydrocortisone dose was adjusted according to clinical response.

Study Design	Methods	Results	Limitations and Interpretation
Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19: A Randomized Clinical Trial⁵, continued			
	<p>Primary Endpoint:</p> <ul style="list-style-type: none"> Treatment failure (defined as death or persistent dependency on mechanical ventilation or high-flow oxygen) by Day 21 <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> Need for intubation, rescue strategies, or oxygenation (i.e., change in PaO₂/FiO₂) Nosocomial infections on Day 28 Clinical status on Day 21 	<p>intubation vs. 12 of 16 (75%) in placebo group.</p> <ul style="list-style-type: none"> 3 SAEs were reported (cerebral vasculitis, cardiac arrest due to PE, and intra-abdominal hemorrhage from anticoagulation for PE); all occurred in the hydrocortisone group, but none were attributed to the intervention. There was no difference between the groups in proportion of patients with nosocomial infections on Day 28. In post hoc analysis, clinical status on Day 21 did not significantly differ between the groups except for fewer deaths in the hydrocortisone group (14.7% of patients died vs. 27.4% in placebo group; <i>P</i> = 0.06): By Day 21, 57.3% of patients in hydrocortisone group vs. 43.8% in placebo group were discharged from the ICU and 22.7% in hydrocortisone group vs. 23.3% in placebo group were still mechanically ventilated. 	
Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial (CAPE COD)⁶			
<p>Randomized, embedded, multifactorial, adaptive platform trial of patients with severe COVID-19 (n = 403)</p> <p>Countries: Multinational</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> Aged ≥18 years Presumed or confirmed SARS-CoV-2 infection ICU admission for respiratory or cardiovascular organ support <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> Presumed imminent death Systemic corticosteroid use >36 hours since ICU admission 	<p>Number of Participants:</p> <ul style="list-style-type: none"> mITT analysis (n = 384): Fixed-dose hydrocortisone (n=137), shock-based hydrocortisone (n = 146), and no hydrocortisone (n = 101) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> Mean age was 60 years. 71% of patients were men. Mean BMI was 29.7–30.9. 50% to 64% of patients received mechanical ventilation. 	<p>Limitations:</p> <ul style="list-style-type: none"> Early termination following release of RECOVERY study results Randomized study, but open label <p>Interpretation:</p> <ul style="list-style-type: none"> Corticosteroids did not significantly increase support-free days in either the fixed-dose hydrocortisone or the shock-dependent hydrocortisone group, although the early termination of the trial led to limited power to detect difference between the study arms.

Study Design	Methods	Results	Limitations and Interpretation
Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial (CAPE COD)⁶, continued			
	<p>Interventions:</p> <ul style="list-style-type: none"> Hydrocortisone 50 mg 4 times daily for 7 days Septic shock-based hydrocortisone 50 mg 4 times daily for the duration of shock No hydrocortisone <p>Primary Endpoint:</p> <ul style="list-style-type: none"> Days free of respiratory and cardiovascular organ support up to Day 21. (For this ordinal outcome, patients who died were assigned -1 day.) <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> In-hospital mortality SAEs 	<p>Primary Outcome:</p> <ul style="list-style-type: none"> No difference between the groups in organ-support free-days at Day 21 (median of 0 days in each group). Compared to the no hydrocortisone group, median adjusted OR for the primary outcome: <ul style="list-style-type: none"> OR 1.43 (95% credible interval, 0.91–2.27) with 93% Bayesian probability of superiority for the fixed-dose hydrocortisone group OR 1.22 (95% credible interval, 0.76–1.94) with 80% Bayesian probability of superiority for the shock-based hydrocortisone group <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> No difference between the groups in mortality; 30%, 26%, and 33% of patients died in the fixed-dose, shock-based, and no hydrocortisone groups, respectively. SAEs reported in 3%, 3%, and 1% of patients in the fixed-dose, shock-based, and no hydrocortisone groups, respectively. 	
Efficacy Evaluation of Early, Low-Dose, Short-Term Corticosteroids in Adults Hospitalized with Non-Severe COVID-19 Pneumonia: A Retrospective Cohort Study⁷			
<p>Retrospective cohort study in patients with nonsevere COVID-19 pneumonia and propensity score-matched controls (n = 55 matched case-control pairs)</p> <p>Country: China</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> Confirmed COVID-19 Pneumonia on chest CT scan Aged ≥16 years <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> Severe pneumonia defined as having any of the following: respiratory distress, respiratory rates >30 breaths/min, SpO₂ <93%, oxygenation index <300 mm Hg, mechanical ventilation, or shock 	<p>Number of Participants:</p> <ul style="list-style-type: none"> Corticosteroids (n = 55): IV methylprednisolone (n=50) and prednisone (n = 5) No corticosteroids (n = 55 matched controls chosen from 420 patients who did not receive corticosteroids) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> Median age was 58–59 years. Median oxygen saturation was 95%. 42% of patients in corticosteroids group and 46% in no corticosteroids group had comorbidities, including 35% to 36% with hypertension and 11% to 13% with diabetes. 	<p>Limitations:</p> <ul style="list-style-type: none"> Retrospective, case-control study Small sample size (55 case-control pairs) Corticosteroid therapy was selected preferentially for patients who had more risk factors for severe progression of COVID-19; the propensity score matching may not have adjusted for some of the unmeasured confounders.

Study Design	Methods	Results	Limitations and Interpretation
Efficacy Evaluation of Early, Low-Dose, Short-Term Corticosteroids in Adults Hospitalized with Non-Severe COVID-19 Pneumonia: A Retrospective Cohort Study⁷, continued			
	<ul style="list-style-type: none"> • Immediate ICU admission upon hospitalization • Use of corticosteroids after progression to severe disease <p>Interventions:</p> <ul style="list-style-type: none"> • Early, low-dose corticosteroids: <ul style="list-style-type: none"> • IV methylprednisolone 20 mg/day or 40 mg/day for 3–5 days • PO prednisone 20 mg/day for 3 days • No corticosteroids <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Rates of severe disease and death <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> • Duration of fever • Virus clearance time • Length of hospital stay • Use of antibiotics 	<p>Primary Outcomes:</p> <ul style="list-style-type: none"> • 7 patients (12.7%) in the corticosteroids group developed severe disease vs. 1 (1.8%) in the no corticosteroids group ($P = 0.03$); time to severe disease: HR 2.2 (95% CI, 2.0–2.3; $P < 0.001$). • There was 1 death in the methylprednisolone group vs. none in the no corticosteroids group. <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> • Each of the following outcomes was longer in the corticosteroids group than in the no corticosteroids group ($P < 0.001$ for each outcome): duration of fever (5 vs. 3 days), virus clearance time (18 vs. 11 days), and length of hospital stay (23 vs. 15 days). • More patients in the corticosteroids group than in the no corticosteroids group were prescribed antibiotics (89% vs. 24%) and antifungal therapy (7% vs. 0%). 	<ul style="list-style-type: none"> • Selection bias in favor of the no corticosteroids group may have been introduced by excluding patients who used corticosteroids after progression to severe disease from the study. <p>Interpretation:</p> <ul style="list-style-type: none"> • In this nonrandomized, case-control study, methylprednisolone therapy in patients with nonsevere COVID-19 pneumonia was associated with worse outcomes, but this finding is difficult to interpret because of potential confounding factors. • It is unclear whether the results for methylprednisolone therapy can be generalized to therapy with other corticosteroids.

Key: AE = adverse event; ARDS = acute respiratory distress syndrome; AZM = azithromycin; BMI = body mass index; CT = computerized tomography; ECMO = extracorporeal membrane oxygenation; EU = European Union; HCQ = hydroxychloroquine; ICU = intensive care unit; IL = interleukin; ITT = intention-to-treat; IV = intravenous; LPV/RTV = lopinavir/ritonavir; mITT = modified intention-to-treat; the Panel = the COVID-19 Treatment Guidelines Panel; PaO₂/FiO₂ = ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; PE = pulmonary embolism; PEEP = positive end-expiratory pressure; PO = oral; RCT = randomized controlled trial; RDV = remdesivir; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOC = standard of care; SOFA = sequential organ failure assessment; SpO₂ = saturation of oxygen; WHO = World Health Organization

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Fluvoxamine

Last Updated: April 21, 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 Further studies are needed to establish whether the anti-inflammatory effects of fluvoxamine observed in nonclinical studies also occur in humans beings and are clinically relevant in the setting of COVID-19.

Recommendation

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

Clinical Trial Data

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

In this contactless, double-blind, placebo-controlled randomized trial, nonhospitalized adults with mild COVID-19 confirmed by SARS-CoV-2 polymerase chain reaction (PCR) assay within 7 days of symptom onset were randomized to receive fluvoxamine up to 100 mg three times daily or matching placebo for 15 days. The primary endpoint was clinical deterioration (defined as having dyspnea or hospitalization for dyspnea or pneumonia and oxygen saturation [SpO_2] $<92\%$ on room air or requiring supplemental oxygen to attain $\text{SpO}_2 \geq 92\%$) within 15 days of randomization. Participants self-assessed their blood pressure, temperature, oxygen saturation, and COVID-19 symptoms and reported the information by email twice daily.³

Participant Characteristics

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

Results

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

Limitations

- The study had a small sample size.

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

Interpretation

In this small placebo-controlled trial, none of the participants who received fluvoxamine and six (7.3%) of those who received placebo reached the primary endpoint. However, due to the study's reliance on participant self-reports and missing data, it is difficult to draw definitive conclusions about the efficacy of fluvoxamine for the treatment of COVID-19.³

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

A prospective, nonrandomized observational cohort study evaluated fluvoxamine for the treatment of COVID-19 in 133 outpatients who tested positive for SARS-CoV-2 antigen with the result confirmed by a PCR test. The trial was conducted in an occupational setting during an outbreak of COVID-19. Patients were offered the option of receiving fluvoxamine 50 mg twice daily for 14 days or no therapy.⁴

Patient Characteristics

- Of the 133 participants, 65 opted to take fluvoxamine and 48 did not.
- More of the patients who did not take fluvoxamine had hypertension. In addition, more of those who were Latinx and more of those who were initially symptomatic opted to take fluvoxamine.

Results

- At Day 14, none of the patients who received fluvoxamine versus 40% of those who did not had persistent symptoms (e.g., anxiety, difficulty concentrating, fatigue) ($P < 0.001$).
- By Day 14, none of the fluvoxamine-treated patients were hospitalized; six patients who did not receive fluvoxamine were hospitalized, including two patients who required care in the intensive care unit.
- No serious adverse events were reported following receipt of fluvoxamine.

Limitations

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

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

Additional studies, including a Phase 3 randomized controlled trial (*ClinicalTrials.gov* Identifier: [NCT04668950](https://clinicaltrials.gov/ct2/show/study/NCT04668950)), are ongoing to provide more specific evidence-based guidance on the role of fluvoxamine for the treatment of COVID-19.

Adverse Effects, Monitoring, and Drug-Drug Interactions

When fluvoxamine is used to treat psychiatric conditions, the most common adverse effect is nausea, but adverse effects can include other gastrointestinal effects (e.g., diarrhea, indigestion), neurologic effects (e.g., asthenia, insomnia, somnolence), dermatologic reactions (sweating), and rarely suicidal ideation.

Fluvoxamine is a cytochrome P450 (CYP) D6 substrate and a potent inhibitor of CYP1A2 and 2C19 and a moderate inhibitor of CYP2C9, 2D6, and 3A4.⁵ Fluvoxamine may enhance the anticoagulant effects of antiplatelets and anticoagulants. In addition, it can enhance the serotonergic effects of other SSRIs

or monoamine oxidase inhibitors (MAOIs) resulting in serotonin syndrome. Fluvoxamine should not be used within 2 weeks of receipt of other SSRIs or MAOIs and should be used with caution with other QT-interval prolonging medications.

Considerations in Pregnancy

Fluvoxamine is not thought to increase the risk of congenital abnormalities; however, the data on its use in pregnancy are limited.^{6,7} A small, increased risk of primary persistent pulmonary hypertension in the newborn associated with SSRI use in the late third trimester has not been excluded, although the absolute risk is likely low.⁸ The risk of fluvoxamine use in pregnancy for the treatment of COVID-19 should be balanced with the potential benefit.

Considerations in Children

Fluvoxamine is approved by the FDA for the treatment of obsessive compulsive disorder in children aged ≥ 8 years.⁹ Adverse effects due to SSRI use seen in children are similar to those seen in adults, although children and adolescents appear to have higher rates of behavioral activation and vomiting than adults.¹⁰ There are no data on the use of fluvoxamine for the prevention or treatment of COVID-19 in children.

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Immunoglobulins: Non-SARS-CoV-2 Specific

Last Updated: July 17, 2020

Recommendation

- The COVID-19 Treatment Guidelines Panel **recommends against** the use of non-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-specific **intravenous immunoglobulin (IVIG)** for the treatment of COVID-19, except in a clinical trial (**AIII**). This recommendation **should not preclude** the use of IVIG when otherwise indicated for the treatment of complications that arise during the course of COVID-19.

Rationale for Recommendation

It is unknown whether products derived from the plasma of donors without confirmed SARS-CoV-2 infection contain high titer of SARS-CoV-2 neutralizing antibodies. Furthermore, although other blood components in IVIG may have general immunomodulatory effects, it is unclear whether these theoretical effects will benefit patients with COVID-19.

Clinical Data for COVID-19

This study has not been peer reviewed.

A retrospective, non-randomized cohort study of IVIG for the treatment of COVID-19 was conducted across eight treatment centers in China between December 2019 and March 2020. The study showed no difference in 28-day or 60-day mortality between 174 patients who received IVIG and 151 patients who did not receive IVIG.¹ More patients in the IVIG group had severe disease at study entry (71 patients [41%] with critical status in the IVIG group vs. 32 patients [21%] in the non-IVIG group). The median hospital stay was longer in the IVIG group (24 days) than in the non-IVIG group (16 days), and the median duration of disease was also longer (31 days in the IVIG group vs. 23 days in the non-IVIG group). A subgroup analysis that was limited to the critically ill patients suggested a mortality benefit at 28 days, which was no longer significant at 60 days.

The results of this study are difficult to interpret because of important limitations in the study design. In particular, patients were not randomized to receive either IVIG or no IVIG, and the patients in the IVIG group were older and more likely to have coronary heart disease than those in the non-IVIG group. In addition, the IVIG group had a higher proportion of patients with severe COVID-19 disease at study entry. Patients in both groups also received many concomitant therapies for COVID-19.

Considerations in Pregnancy

IVIG is commonly used in pregnancy for other indications such as immune thrombocytopenia with an acceptable safety profile.^{2,3}

Considerations in Children

IVIG has been widely used in children for the treatment of a number of conditions, including Kawasaki disease, and is generally safe.⁴ IVIG has been used in pediatric patients with COVID-19 and multiorgan inflammatory syndrome in children (MIS-C), especially those with a Kawasaki disease-like presentation, but the efficacy of IVIG in the management of MIS-C is still under investigation.

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Interferons (Alfa, Beta)

Last Updated: August 27, 2020

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

Recommendation

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

Rationale

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

Clinical Data for COVID-19

Interferon Beta-1a

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

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

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

An open-label, Phase 2 clinical trial randomized 127 participants (median age of 52 years) 2:1 to combination antiviral therapy or lopinavir/ritonavir. In the combination antiviral therapy group, the treatment regimen differed by time from symptom onset to hospital admission. Participants hospitalized within 7 days of symptom onset (n = 76) were randomized to triple drug therapy (interferon beta-1b 8 million units administered subcutaneously every other day for up to 7 days total, lopinavir/ritonavir,

and ribavirin); those hospitalized ≥ 7 days after symptom onset ($n = 51$) were randomized to double therapy (lopinavir/ritonavir and ribavirin) because of concerns regarding potential inflammatory effects of interferon. Patients in the control group received lopinavir/ritonavir alone regardless of the time from symptom onset to hospitalization. The study participants were patients in Hong Kong with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection who were hospitalized, regardless of disease severity, until they had two negative nasopharyngeal (NP) swab tests.

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

Interferon Alfa-2b

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

Clinical Data for SARS and MERS

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

In a retrospective observational analysis of 350 critically ill patients with MERS⁶ from 14 hospitals in Saudi Arabia, the mortality rate was higher among patients who received ribavirin and interferon (beta-1a, alfa-2a, or alfa-2b) than among those who did not receive either drug.

A randomized clinical trial that included 301 patients with acute respiratory distress syndrome¹⁰ found that intravenous interferon beta-1a had no benefit over placebo as measured by ventilator-free days over a 28-day period (median of 10.0 days in the interferon beta-1a group vs. 8.5 days in the placebo group) or mortality (26.4% in the interferon beta-1a group vs. 23.0% in the placebo group).

Clinical Trials

See [ClinicalTrials.gov](https://clinicaltrials.gov) for a list of [ongoing clinical trials for interferon and COVID-19](#).

Adverse Effects

The most frequent adverse effects of interferon alfa include flu-like symptoms, nausea, fatigue, weight loss, hematological toxicities, elevated transaminases, and psychiatric problems (e.g., depression and

suicidal ideation). Interferon beta is better tolerated than interferon alfa.^{11,12}

Drug-Drug Interactions

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

Considerations in Pregnancy

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

Considerations in Children

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

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Interleukin-1 Inhibitors

Last Updated: July 17, 2020

Recommendation

- There are insufficient data to recommend for or against the use of interleukin (IL)-1 inhibitors, such as **anakinra**, for the treatment of COVID-19.

Rationale

There are case series data but no clinical trial data on the use of IL-1 inhibitors in patients with COVID-19.

Anakinra is a recombinant human IL-1 receptor antagonist. It is approved by the Food and Drug Administration (FDA) to treat rheumatoid arthritis and cryopyrin-associated periodic syndromes, specifically neonatal-onset multisystem inflammatory disease.¹ It is also used off-label for severe chimeric antigen receptor T cell (CAR T-cell)-mediated cytokine release syndrome (CRS) and macrophage activation syndrome (MAS)/secondary hemophagocytic lymphohistiocytosis.

Rationale for Use in Patients with COVID-19

Endogenous IL-1 is elevated in patients with COVID-19 and other conditions, such as severe CAR T-cell-mediated CRS. Case reports and case series have described favorable responses to anakinra in patients with these syndromes, including a survival benefit in patients with sepsis and reversal of cytokine storm after tocilizumab failure in adults with MAS.^{2,3}

Clinical Data for COVID-19

- A case-control study compared outcomes in 52 consecutive patients with COVID-19 treated with anakinra and 44 historical controls. The patients in both groups were all admitted to the same hospital in Paris, France. Case patients were consecutive admissions from March 24 to April 6, 2020, with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or lung infiltrates on chest imaging typical of COVID-19, and either significant hypoxia ($\text{SpO}_2 \leq 93\%$ with $\geq 6\text{L}/\text{min O}_2$) or worsening hypoxia ($\text{SpO}_2 \leq 93\%$ with $>3\text{L}/\text{min O}_2$ and a loss of $\geq 3\%$ of O_2 saturation on room air in the previous 24 hours). The historic controls were patients who fulfilled the same eligibility criteria and admitted to the hospital during the same period. As standard of care for both groups, some patients received hydroxychloroquine, azithromycin, or parenteral beta-lactam antibiotics. Anakinra was dosed as 100 mg subcutaneous (SQ) twice daily for 72 hours, followed by anakinra 100 mg SQ daily for 7 days. Clinical characteristics were similar between the groups, except that the cases had a lower mean body mass index than the controls ($25.5 \text{ kg}/\text{m}^2$ vs. $29.0 \text{ kg}/\text{m}^2$, respectively), longer duration of symptoms (mean of 8.4 days for cases vs. 6.2 days for controls), and a higher frequency of hydroxychloroquine use (90% for cases vs. 61% for controls) and azithromycin use (49% for cases vs. 34% for controls). The primary outcome of admission to the intensive care unit for mechanical ventilation or death occurred among 13 case patients (25%) and 32 control patients (73%) (hazard ratio 0.22; 95% confidence interval, 0.11 to 0.41). However, within the first 2 days of follow up, in the control group, six patients (14%) had died and 19 patients (43%) had reached the composite primary outcome, which further limited intragroup comparisons and specifically analyses of time to event. C-reactive protein (CRP) levels decreased by Day 4 among those receiving anakinra. Thromboembolic events occurred in 10 patients (19%) who received anakinra and in five control patients (11%). The clinical implications of these findings are uncertain due to limitations in the

study design related to unmeasured confounding combined with the very high early event rate among the retrospective controls.⁴

- A single-center, retrospective cohort study compared outcomes in 29 patients following open-label use of anakinra to outcomes in 16 historical controls enrolled at the same medical center in Italy. All patients had COVID-19 with moderate to severe acute respiratory distress syndrome (ARDS) that required non-invasive ventilation and evidence of hyperinflammation (CRP \geq 100 mg/L and/or ferritin \geq 900 ng/mL). High-dose intravenous anakinra 5 mg/kg twice daily was administered for a median of 9 days, followed by SQ administration of anakinra 100 mg twice daily for 3 days to avoid inflammatory relapses. Patients in both the anakinra and control groups received hydroxychloroquine and lopinavir/ritonavir. In the anakinra group, reductions in CRP levels were noted over several days following anakinra initiation, and the 21-day survival rate was higher than in the control group (90% vs. 56%, respectively; $P = 0.009$). However, the patients in the anakinra group were younger than those in the control group (median age 62 years vs. 70 years, respectively), and fewer patients in the anakinra group had chronic kidney disease. High-dose anakinra was discontinued in seven patients (24%) because of adverse events (four patients developed bacteremia and three patients had elevated liver enzymes); however, retrospective assessment showed that these events occurred with similar frequency in the control group. An additional group of seven patients received low-dose SQ anakinra 100 mg twice daily; however, treatment in this group was stopped after 7 days because of lack of clinical or anti-inflammatory effects.⁵
- Other small case series have reported anakinra use for the treatment of COVID-19 and anecdotal evidence of improvement in outcomes.⁶

Clinical Trials

See [ClinicalTrials.gov](https://clinicaltrials.gov) for a list of clinical trials evaluating anakinra for the treatment of COVID-19.

Adverse Effects

Anakinra was not associated with any significant safety concerns when used in clinical trials for the treatment of sepsis.⁷⁻⁹ Increased rates of infection were reported with prolonged anakinra use in combination with tumor necrosis factor-alpha blockade, but not with short-term use.¹⁰

Considerations in Pregnancy

There is limited evidence on which to base a recommendation in pregnancy, but unintentional first trimester exposure is unlikely to be harmful.¹¹

Considerations in Children

Anakinra has been used extensively in the treatment of severely ill children with complications of rheumatologic conditions, including MAS. Pediatric data on the use of anakinra in ARDS/sepsis are limited.

Drug Availability

Procuring anakinra may be a challenge at some hospitals in the United States. Anakinra is FDA-approved only for SQ injection.

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Interleukin-6 Inhibitors

Last Updated: April 21, 2021

Interleukin (IL)-6 is a pleiotropic, proinflammatory cytokine produced by a variety of cell types, including lymphocytes, monocytes, and fibroblasts. Infection by the severe acute respiratory syndrome-associated coronavirus (SARS-CoV) induces a dose-dependent production of IL-6 from bronchial epithelial cells.¹ COVID-19-associated systemic inflammation and hypoxic respiratory failure can be associated with heightened cytokine release, as indicated by elevated blood levels of IL-6, C-reactive protein (CRP), D-dimer, and ferritin.²⁻⁴ It is hypothesized that modulating the levels of IL-6 or its effects may reduce the duration and/or severity of COVID-19 illness.

There are two classes of Food and Drug Administration (FDA)-approved IL-6 inhibitors: anti-IL-6 receptor monoclonal antibodies (e.g., sarilumab, tocilizumab) and anti-IL-6 monoclonal antibodies (i.e., siltuximab). These drugs have been evaluated for the management of patients with COVID-19 who have systemic inflammation. The COVID-19 Treatment Guidelines Panel's (the Panel's) recommendations on the use of IL-6 inhibitors in patients with COVID-19 and related clinical data to date are described below.

Recommendations

- The Panel recommends using **tocilizumab** (single intravenous [IV] dose of tocilizumab 8 mg/kg actual body weight up to 800 mg) **in combination with dexamethasone** (6 mg daily for up to 10 days) in certain hospitalized patients who are exhibiting rapid respiratory decompensation due to COVID-19. These patients are:
 - Recently hospitalized patients (i.e., within first 3 days of admission) who have been admitted to the intensive care unit (ICU) within the prior 24 hours and who require invasive mechanical ventilation, noninvasive ventilation, or high-flow nasal canula (HFNC) oxygen (>0.4 FiO₂/30 L/min of oxygen flow) (**BIIa**); *or*
 - Recently hospitalized patients (i.e., within first 3 days of admission) not admitted to the ICU who have rapidly increasing oxygen needs and require noninvasive ventilation or HFNC oxygen and who have significantly increased markers of inflammation (CRP ≥ 75 mg/L) (**BIIa**).
- For hospitalized patients with hypoxemia who require conventional oxygen therapy, there is insufficient evidence to specify which of these patients would benefit from the addition of tocilizumab. Some Panel members would also give tocilizumab to patients who are exhibiting rapidly increasing oxygen needs while on dexamethasone and have a CRP ≥ 75 mg/L, but who do not yet require noninvasive ventilation or HFNC oxygen as described above.
- There are insufficient data for the Panel to recommend either for or against the use of sarilumab for hospitalized patients with COVID-19 who are within 24 hours of admission to the ICU and who require invasive mechanical ventilation, noninvasive ventilation, or high-flow oxygen (>0.4 FiO₂/30 L/min of oxygen flow).
- The Panel **recommends against** the use of anti-IL-6 monoclonal antibody therapy (i.e., **siltuximab**) for the treatment of COVID-19, except in a clinical trial (**BI**).

Additional Considerations

- Tocilizumab **should be avoided** in patients who are significantly immunosuppressed, particularly in those with recent use of other biologic immunomodulating drugs, and in patients who have alanine aminotransferase >5 times the upper limit of normal; high risk for gastrointestinal perforation; an uncontrolled serious bacterial, fungal, or non-SARS-CoV-2 viral

infection; absolute neutrophil count <500 cells/ μ L; platelet count <50,000 cells/ μ L; or known hypersensitivity to tocilizumab.

- Tocilizumab should only be given in combination with a course of dexamethasone (or an alternative [corticosteroid](#) at a dose equivalency to dexamethasone 6 mg) therapy.
- Some clinicians may assess the patient's clinical response to dexamethasone before deciding whether tocilizumab is needed.
- Although some patients in the Randomised, Embedded, Multi-factorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) and the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial received a second dose of tocilizumab at the discretion of treating physicians, there are insufficient data to indicate which patients, if any, would benefit from an additional dose of tocilizumab.
- Cases of severe and disseminated strongyloidiasis have been reported with use of tocilizumab and corticosteroids in patients with COVID-19.^{5,6} Prophylactic treatment with ivermectin should be considered for patients who are from strongyloidiasis endemic areas.⁷

Rationale

The results of the RECOVERY trial and REMAP-CAP provide consistent evidence that tocilizumab, when administered with corticosteroids, offers a modest mortality benefit in certain patients with COVID-19 who are severely ill, rapidly deteriorating with increasing oxygen needs, and have a significant inflammatory response. However, the Panel found it challenging to define the specific patient population(s) that would benefit from this intervention. See an overview of the clinical trial data on the use of tocilizumab in patients with COVID-19 below.

Sarilumab and tocilizumab have a similar mechanism of action. However, in REMAP-CAP, the number of participants who received sarilumab was relatively small. Moreover, the trial evaluated sarilumab for IV administration, which is not the approved formulation in the United States. The results of randomized controlled trials of sarilumab that are underway will further define the role sarilumab plays in the treatment of COVID-19.

There are only limited data describing the potential for efficacy of siltuximab in patients with COVID-19.¹¹

Anti-Interleukin-6 Receptor Monoclonal Antibodies

Tocilizumab

Tocilizumab is a recombinant humanized anti-IL-6 receptor monoclonal antibody that is approved by the FDA for use in patients with rheumatologic disorders and cytokine release syndrome (CRS) induced by chimeric antigen receptor T cell (CAR T-cell) therapy. Tocilizumab can be dosed for IV or subcutaneous (SQ) injection. The IV formulation should be used to treat CRS.⁸

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 4b](#).

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).⁹⁻¹¹ For example, trials that reported a treatment benefit of tocilizumab enrolled patients who

were receiving higher levels of oxygen support (e.g., HFNC oxygen, noninvasive ventilation, invasive mechanical ventilation) and/or included more patients who used corticosteroids.^{12,13} Subsequently, REMAP-CAP and the RECOVERY trial—the two largest randomized controlled tocilizumab trials—reported a mortality benefit of tocilizumab in certain patients, including patients exhibiting rapid respiratory decompensation associated with an inflammatory response. REMAP-CAP enrolled a narrowly defined population of critically ill patients who were enrolled within 24 hours of starting respiratory support in an ICU and randomized to receive open-label tocilizumab or usual care.¹⁴ The RECOVERY trial enrolled hospitalized patients with COVID-19 into an open label, platform trial of several treatment options;¹⁵ a subset of participants with hypoxemia and CRP ≥ 75 mg/L were offered enrollment into a second randomization to tocilizumab versus usual care. Additional findings from REMAP-CAP and the RECOVERY trial and the rationale for using tocilizumab in certain hospitalized patients who are exhibiting rapid respiratory decompensations due to COVID-19 can be found in [Therapeutic Management of Adults With COVID-19](#).

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

Clinical Trials

Ongoing trials are evaluating the use of tocilizumab for the treatment of COVID-19. See [ClinicalTrials.gov](#) for the latest information.

Adverse Effects

The primary laboratory abnormalities reported with tocilizumab treatment are elevated liver enzyme levels that appear to be dose dependent. Neutropenia or thrombocytopenia are uncommon. Additional adverse effects, such as risk for serious infections (e.g., tuberculosis [TB], bacterial or fungal infections) and bowel perforation, have been reported only in the context of tocilizumab use for the treatment of chronic disease.

Considerations in Pregnancy

There are insufficient data to determine whether there is a tocilizumab-associated risk for major birth defects or miscarriage. Monoclonal antibodies are actively transported across the placenta as pregnancy progresses (with greatest transfer during the third trimester) and may affect immune responses in utero in the exposed fetus. Given the paucity of data, current recommendations advise against the use of tocilizumab during pregnancy.¹⁶ Decisions about tocilizumab administration during pregnancy must include shared decision-making between the pregnant individual and their health care provider, considering potential maternal benefit and fetal risks.

Considerations in Children

There are no systematic observational or randomized controlled trial data available on the effectiveness of tocilizumab for the treatment of COVID-19 or multisystem inflammatory syndrome in children (MIS-C) in children. Tocilizumab has been used for children with CRS associated with CAR T-cell therapy and systemic and polyarticular juvenile idiopathic arthritis.¹⁷ There are insufficient data for the Panel to recommend either for or against the use of tocilizumab in hospitalized children with COVID-19 or MIS-C.

Sarilumab

Sarilumab is a recombinant humanized anti-IL-6 receptor monoclonal antibody that is approved by the FDA for use in patients with rheumatoid arthritis. It is available as an SQ formulation and is not approved for the treatment of CRS.

Clinical Data for COVID-19

Clinical data for sarilumab (and other IL-6 inhibitors) as treatment for COVID-19, including data from several randomized trials and large observational studies, are summarized in [Table 4b](#).

An adaptive Phase 2 and 3 double-blind, placebo-controlled randomized (2:2:1) trial compared the efficacy and safety of sarilumab 400 mg IV and sarilumab 200 mg IV versus placebo in patients hospitalized 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.¹⁸ Preliminary efficacy results from REMAP-CAP for sarilumab were similar to those for tocilizumab. Compared to placebo, sarilumab reduced both mortality and time to ICU discharge, and increased the number of organ support-free days; however, the number of participants who received sarilumab in this trial was relatively small, limiting the conclusions and implications of these findings.¹⁹

Clinical Trials

Ongoing trials are evaluating the use of sarilumab for the treatment of COVID-19. See [ClinicalTrials.gov](#) for the latest information.

Adverse Effects

The primary lab abnormalities that have been reported with sarilumab treatment are transient and/or reversible elevations in liver enzymes that appear to be dose dependent and rare occurrences of neutropenia and thrombocytopenia. Risk for serious infections (e.g., TB, bacterial or fungal infections) and bowel perforation have been reported only with long-term use of sarilumab.

Considerations in Pregnancy

There are insufficient data to determine whether there is a sarilumab-associated risk for major birth defects or miscarriage. Monoclonal antibodies are actively transported across the placenta as pregnancy progresses (with greatest transfer during the third trimester) and may affect immune responses in utero in the exposed fetus.

Considerations in Children

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

Drug Availability

The SQ formulation of sarilumab is not approved for the treatment of CRS. The IV formulation is not approved by the FDA, but it is being studied in a clinical trial of hospitalized patients with COVID-19.

Anti-Interleukin-6 Monoclonal Antibody

Siltuximab

Siltuximab is a recombinant human-mouse chimeric monoclonal antibody that binds IL-6 and is approved by the FDA for use in patients with 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 describing the efficacy of siltuximab in patients with COVID-19.²⁰ 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](https://www.clinicaltrials.gov) for a list of current clinical trials for siltuximab and COVID-19.

Adverse Effects

The primary adverse effects reported for siltuximab have been related to rash. Additional adverse effects (e.g., serious bacterial infections) have been reported only with long-term dosing of siltuximab once every 3 weeks.

Considerations in Pregnancy

There are insufficient data to determine whether there is a siltuximab-associated risk for major birth defects or miscarriage. Monoclonal antibodies are transported across the placenta as pregnancy progresses (with greatest transfer during the third trimester) and may affect immune responses in the exposed fetus.

Considerations in Children

The safety and efficacy of siltuximab have not been established in pediatric patients.

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Table 4b. Interleukin-6 Inhibitors: Selected Clinical Data

Last Updated April 21, 2021

The clinical trials described in this table do not represent all the trials that the Panel reviewed while developing the recommendations for IL-6 inhibitors. The studies summarized below are those that have had the greatest impact on the Panel's recommendations.

Study Design	Methods	Results	Limitations and Interpretation
Tocilizumab in Hospitalized Patients With COVID-19 (RECOVERY Trial)¹			
<p>Second randomization of the RECOVERY trial, an open-label, randomized controlled-platform trial assessing several treatments in hospitalized patients with COVID-19 in the United Kingdom (n = 4,116; 19% of all RECOVERY trial participants [n = 21,550])</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Suspected or laboratory-confirmed COVID-19 • Participant within 21 days of enrollment into the initial randomization of the RECOVERY trial • Hypoxia evidenced by SpO₂ <92% on room air or receipt of supplemental oxygen • CRP ≥75 mg/L <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Tocilizumab unavailable at participating hospital • Evidence of active non-SARS-CoV-2 infection, including TB or other bacterial, fungal, or viral infection <p>Interventions</p> <p><i>1: 1 Randomization:</i></p> <ul style="list-style-type: none"> • Single dose of tocilizumab 8 mg/kg, and possible second dose, <i>or</i> • Usual care <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • All-cause mortality through 28 days <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> • Time to discharge alive • Among those not on mechanical ventilation at enrollment, receipt of mechanical ventilation or death 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • Tocilizumab (n = 2,022) and usual care (n = 2,094) • Recruitment period: April 14, 2020, through January 24, 2021 <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Mean age was 63.6 years. • 67% of participants were men. • 68% of participants were white. • 94% of participants had PCR-confirmed SARS-CoV-2 infection. • Median time from hospitalization until enrollment was 2 days (IQR 1–5 days). • Median CRP 143 mg/L (IQR 107–204 mg/L). • At baseline, 45% of participants were on conventional oxygen, 41% on HFNC/noninvasive ventilation, and 14% on mechanical ventilation. • At enrollment, 82% of participants were taking corticosteroids. <p>Primary Outcomes:</p> <ul style="list-style-type: none"> • Mortality by Day 28 was lower in the tocilizumab arm than in the usual care arm (29% vs. 33%; rate ratio 0.86; 95% CI, 0.77–0.96). • Subgroup analysis: Among those who required mechanical ventilation at baseline, mortality by Day 28 was similar in the tocilizumab and usual care arms (47% vs. 48%). 	<p>Limitations:</p> <ul style="list-style-type: none"> • Open-label study • Limited collection of AEs • Only a small proportion of the participants were from ethnic or racial minority groups. • Difficult to define exact subset of hospitalized patients in full RECOVERY cohort who were subsequently selected for secondary randomization/tocilizumab trial. • Arbitrary cut off of CRP ≥75 mg/L <p>Interpretation:</p> <ul style="list-style-type: none"> • Among hospitalized patients with severe or critical COVID-19 with hypoxia and elevated CRP levels (≥75 mg/L), tocilizumab was associated with reduced all-cause mortality and shorter time to discharge.

Study Design	Methods	Results	Limitations and Interpretation
Tocilizumab in Hospitalized Patients With COVID-19 (RECOVERY Trial)¹, continued			
		<p>Secondary Outcomes:</p> <ul style="list-style-type: none"> • The proportion of patients who were discharged alive within 28 days was greater in tocilizumab arm than usual care arm (54% vs. 47%; rate ratio 1.22; 95% CI, 1.12–1.34). • Among those not on mechanical ventilation at baseline, the percentage of participants who met the secondary outcome of mechanical ventilation or death was lower in the tocilizumab arm than in the usual care arm (33% vs. 38%; risk ratio 0.85; 95% CI, 0.78–0.93). 	
Interleukin-6 Receptor Antagonists in Critically Ill Patients With COVID-19—Preliminary Report (REMAP-CAP)²			
<p>Multinational RCT in critically ill, hospitalized patients with COVID-19 (n = 865)</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Suspected or laboratory-confirmed COVID-19 • Admitted to ICU and receiving respiratory or cardiovascular organ support <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • >24 hours since admission to ICU • Presumption of imminent death with lack of commitment to full support • Immunosuppression • ALT >5 times ULN <p>Interventions</p> <p><i>1:1 Randomization:</i></p> <ul style="list-style-type: none"> • Single dose of tocilizumab 8 mg/kg, and possible second dose, plus SOC, <i>or</i> • SOC 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • Tocilizumab plus SOC (n = 353), sarilumab plus SOC (n = 48), and SOC (n = 402) • Recruitment period: April 19 through October 28, 2020 <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Mean age was 61.4 years. • 73% of participants were men. • 72% of participants were White. • 84.4% of participants had a positive SARS-CoV-2 PCR test. • Median time from hospitalization until enrollment: 1.2 days (IQR 0.8–2.8 days). • Median time from ICU admission until enrollment: 13.6 hours (IQR 6.6–19.4 hours). • Baseline level of oxygen support: 28.8% of participants on HFNC, 41.5% on noninvasive ventilation, 29.4% on mechanical ventilation. • In mITT analysis, majority of patients (719 of 792 [90%]) received corticosteroids. 	<p>Limitations:</p> <ul style="list-style-type: none"> • Open-label study • Very few patients randomized to receive sarilumab. • Limited collection of AEs • Low proportion of participants from ethnic/racial minority populations <p>Interpretation:</p> <ul style="list-style-type: none"> • Among the patients with severe/critical COVID-19 who were on high-flow oxygen or noninvasive ventilation or who were mechanically ventilated and within 24 hours of ICU admission, the tocilizumab arm had lower mortality and shorter duration of organ support. This benefit of tocilizumab may be in conjunction with concomitant corticosteroids given the high rate of corticosteroid use among trial participants.

Study Design	Methods	Results	Limitations and Interpretation
Interleukin-6 Receptor Antagonists in Critically Ill Patients With Covid-19—Preliminary Report (REMAP-CAP)², continued			
	<p><i>Alternative 1:1:1 Randomization:</i></p> <ul style="list-style-type: none"> • Single dose of tocilizumab 8 mg/kg, and possible second dose, plus SOC, <i>or</i> • Single dose of sarilumab 400 mg IV plus SOC, <i>or</i> • SOC <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Composite endpoint measured on an ordinal scale combining in-hospital mortality (assigned value: -1) and days free of respiratory or cardiovascular organ support up to Day 21 	<p>Primary Outcomes:</p> <ul style="list-style-type: none"> • Median number of organ support-free days was 10 (IQR -1 to 16 days), 11 (IQR 0–16 days), and 0 (IQR -1 to 15 days) for the tocilizumab, sarilumab, and SOC arms, respectively. • Adjusted OR 1.64 (95% CrI, 1.25–2.14) for tocilizumab arm vs. SOC arm • In-hospital mortality: 28.0% for patients receiving tocilizumab and 35.8% for patients receiving SOC (aOR 1.64; 95% CrI, 1.14–2.35). • Percentage of patients who were not mechanically ventilated who progressed to intubation or death: 41.3% in tocilizumab arm vs. 52.7% in SOC arm. 	<ul style="list-style-type: none"> • REMAP-CAP enrolled patients within 24 hours of ICU level care who were undergoing rapid progression of respiratory dysfunction, a key difference to other tocilizumab trials.
Tocilizumab in Hospitalized Patients With COVID-19 Pneumonia (COVACTA)³			
<p>Multinational, double-blind, placebo-controlled randomized trial in hospitalized patients with COVID-19 (n = 452)</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • COVID-19 confirmed by positive PCR test • Severe COVID-19 pneumonia evidenced by hypoxemia and bilateral chest infiltrates <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Death imminent within 24 hours • Active TB or bacterial, fungal, or viral infection (other than SARS-CoV-2) <p>Interventions</p> <p><i>2:1 Randomization:</i></p> <ul style="list-style-type: none"> • Single dose of tocilizumab 8 mg/kg, and possible second dose, plus SOC • Placebo plus SOC 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • mITT analysis: tocilizumab (n = 294) and placebo (n = 144) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Mean age was 61 years. • 70% of participants were men. • 58% of participants were White. • Median time from symptom onset to randomization: 11 days • Clinical status at baseline by ordinal scale category: 28% of participants on supplemental oxygen (category 3); 30% on HFNC/noninvasive ventilation (category 4); 14% on mechanical ventilation (category 5); and 25% with multiorgan failure (category 6). • Percentage of participants who received corticosteroids at entry or during follow-up: 36% in tocilizumab arm vs. 55% in placebo arm. 	<p>Limitations:</p> <ul style="list-style-type: none"> • Modest power to detect differences in clinical status on Day 28 (the primary outcome) between the study arms • Corticosteroids only used by a subset of patients, which included more patients from the placebo arm; RDV use was rare. • Results mostly generalizable to the sickest patients with COVID-19. <p>Interpretation:</p> <ul style="list-style-type: none"> • There was no difference between tocilizumab and placebo for clinical status (including death) at Day 28 (the primary outcome), but tocilizumab did demonstrate a shorter time to recovery and shorter length of ICU stay (secondary outcomes).

Study Design	Methods	Results	Limitations and Interpretation
Tocilizumab in Hospitalized Patients With COVID-19 Pneumonia (COVACTA)³, continued			
	<p>Primary Endpoint:</p> <ul style="list-style-type: none"> Clinical status at Day 28 (as measured on a 7-category ordinal scale) <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> Time to discharge Length of ICU stay Mortality at Day 28 <p>Ordinal Scale Categories:</p> <ol style="list-style-type: none"> Discharged or ready for discharge Hospitalized on medical ward, not on supplemental oxygen Hospitalized on medical ward, on supplemental oxygen On oxygen by HFNC or noninvasive ventilation On mechanical ventilation Multiorgan failure (with ECMO or mechanical ventilation plus other support) Death 	<p>Primary Outcome:</p> <ul style="list-style-type: none"> There was no significant difference in clinical status on 7-category ordinal scale on Day 28 between the arms: median of category 1 for the tocilizumab arm vs. category 2 for the placebo arm (difference -1.0; 95% CI, -2.5 to 0.0; $P = 0.31$). <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> The time to discharge was shorter in the tocilizumab arm than in the placebo arm (median of 20 days vs. 28 days; HR 1.35; 95% CI, 1.02–1.79). ICU stays were shorter in the tocilizumab arm than in the placebo arm (median of 9.8 days vs. 15.5 days; difference of 5.8 days; 95% CI, -15.0 to -2.9). There was no difference in mortality by Day 28 between the arms (19.7% in tocilizumab arm vs. 19.4% in placebo arm; 95% CI, -7.6 to 8.2; $P = 0.94$). SAEs occurred in 34.9% of patients in the tocilizumab arm vs. 38.5% in the placebo arm. 	
Effect of Tocilizumab on Clinical Outcomes at 15 Days in Patients With Severe or Critical COVID-2019 (TOCIBRAS)⁴			
<p>RCT in severe or critically ill hospitalized patients with COVID-19 in Brazil (n = 129)</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> COVID-19 confirmed by PCR test and radiographic imaging Receiving oxygen to maintain SpO₂ >93% or mechanical ventilation for <24 hours <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> Active, uncontrolled infection Elevated AST or ALT >5 times ULN Reduced renal function with eGFR <30 mL/min/1.72 m² 	<p>Number of Participants:</p> <ul style="list-style-type: none"> Tocilizumab (n = 65) and SOC (n = 64) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> Mean age was 57 years. 68% of participants were men. Mean time from symptom onset to randomization: 10 days Baseline level of oxygen support: 52% of participants on conventional oxygen, 32% on HFNC or noninvasive ventilation, and 16% on mechanical ventilation. 	<p>Limitations:</p> <ul style="list-style-type: none"> Open-label study Relatively small sample size Study was stopped early during the first interim review because of increased risk of death at Day 15. <p>Interpretation:</p> <ul style="list-style-type: none"> In this study population, tocilizumab demonstrated no benefit with respect to mechanical ventilation or death at Day 15 or key secondary outcomes.

Study Design	Methods	Results	Limitations and Interpretation
Effect of Tocilizumab on Clinical Outcomes at 15 Days in Patients With Severe or Critical COVID-2019 (TOCIBRAS)⁴, continued			
	<p>Interventions:</p> <ul style="list-style-type: none"> • Single dose of tocilizumab 8 mg/kg plus SOC • SOC <p>Primary Endpoints:</p> <ul style="list-style-type: none"> • Clinical status at 15 days by ordinal scale category. • Following the statistical analysis plan, the primary outcome for the final analysis was changed to mechanical ventilation or death at Day 15 (categories 6 and 7), because the assumption of proportional odds was not met for the original 7-category ordinal outcome. <p>Key Secondary Endpoint:</p> <ul style="list-style-type: none"> • All-cause mortality to Day 28 <p>Ordinal Scale:</p> <ol style="list-style-type: none"> 1. Not hospitalized, no limitation in activities 2. Not hospitalized, limitation in activities 3. Hospitalized, not receiving supplemental oxygen 4. Hospitalized, receiving supplemental oxygen 5. Hospitalized, receiving NIPPV or high-flow oxygen through a nasal cannula 6. Hospitalized, receiving mechanical ventilation 7. Death 	<ul style="list-style-type: none"> • 86% of participants received corticosteroids. • No patient received RDV, which was unavailable in Brazil during the study period. <p>Primary Outcomes:</p> <ul style="list-style-type: none"> • There was no evidence for a treatment difference in the primary outcome: 28% of participants in the tocilizumab arm vs. 20% in the SOC arm had died or received mechanical ventilation at Day 15 (OR 1.54; 95% CI, 0.66–3.66; $P = 0.32$). • The study was stopped early by recommendation of the Data Monitoring Committee because of increased risk of death in the tocilizumab group: by Day 15, 16.9% of participants in the tocilizumab arm vs. 3.1% in SOC arm had died (OR 6.42; 95% CI, 1.59–43.2). <p>Key Secondary Outcomes:</p> <ul style="list-style-type: none"> • Tocilizumab was associated with a trend towards increased mortality at Day 28 (21% in tocilizumab arm vs. 9% in SOC arm; OR 2.70; 95% CI, 0.97–8.35). • AEs were reported in 43% of patients in the tocilizumab arm and 34% in the SOC arm. 	<ul style="list-style-type: none"> • There were more deaths at Day 15 in the tocilizumab arm than in the SOC arm.

Study Design	Methods	Results	Limitations and Interpretation
Tocilizumab in Nonventilated Patients Hospitalized With COVID-19 Pneumonia (EMPACTA)⁵			
<p>Multinational, double-blind, placebo-controlled, Phase 3 randomized trial in hospitalized patients with COVID-19 (n = 389)</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • COVID-19 confirmed by PCR test and radiographic imaging • Severe COVID-19 pneumonia <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Receipt of noninvasive ventilation or mechanical ventilation <p>Interventions</p> <p><i>2:1 Randomization:</i></p> <ul style="list-style-type: none"> • Single dose of tocilizumab 8 mg/kg plus SOC, possible second dose if not improving, <i>or</i> • Placebo plus SOC <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Mechanical ventilation or death by Day 28 <p>Key Secondary Endpoints:</p> <ul style="list-style-type: none"> • Time to hospital discharge or readiness for discharge • All-cause mortality by Day 28 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • mITT analysis: Tocilizumab (n = 249) and placebo (n = 128) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Mean age was 55.9 years. • 59.2% of participants were men. • 56.0% of participants were Hispanic/Latinx, 14.9% were Black/African American, and 12.7% were American Indian/Alaska Native. • 81% of participants were enrolled at sites in the United States. • Median time from symptom onset to randomization was 8 days. • Percentage of participants who received concomitant medications: <ul style="list-style-type: none"> • Tocilizumab arm: 80.3% received corticosteroids (55.4% received dexamethasone) and 52.6% received RDV • Placebo arm: 87.5% received corticosteroids (67.2% received dexamethasone) and 58.6% received RDV <p>Primary Outcome:</p> <ul style="list-style-type: none"> • By mITT analysis, the cumulative proportion of patients who required mechanical ventilation or who had died by Day 28 was 12.0% in the tocilizumab arm and 19.3% in the placebo arm (HR 0.56; 95% CI, 0.33–0.97; <i>P</i> = 0.04) <p>Key Secondary Outcomes:</p> <ul style="list-style-type: none"> • The median time to hospital discharge or readiness for discharge was 6.0 days in the 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 10.4% (95% CI, 7.2% to 14.9%) in the tocilizumab arm and 8.6% (95% CI, 4.9% to 14.7%) in the placebo arm. • SAEs were reported in 15.2% of patients in the tocilizumab arm and 19.7% in the placebo arm. 	<p>Limitation:</p> <ul style="list-style-type: none"> • Interaction with steroids not explored <p>Interpretation:</p> <ul style="list-style-type: none"> • Among patients with severe COVID-19, tocilizumab lowered rates of mechanical ventilation or death by Day 28 but provided no benefit in 28-day mortality.

Study Design	Methods	Results	Limitations and Interpretation
Efficacy of Tocilizumab in Patients Hospitalized With COVID-19 (BACC Bay Tocilizumab Trial)⁶			
<p>Double-blind, placebo-controlled randomized trial in hospitalized patients with COVID-19 in the United States (n = 243)</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> Hospitalized with COVID-19 confirmed by a positive PCR or serum IgM test Moderate and severe COVID-19 with >2 of the following symptoms: fever >38°C, pulmonary infiltrates, need for oxygen to maintain saturation >92% and also 1 of the following: CRP ≥50 mg/L, D-dimer >1,000 ng/mL, LDH ≥250 U/L, ferritin >500 ng/mL <p>Interventions</p> <p><i>2:1 Randomization:</i></p> <ul style="list-style-type: none"> Tocilizumab 8 mg/kg once plus usual care; or Placebo plus usual care <p>Primary Endpoint:</p> <ul style="list-style-type: none"> Time to intubation or death (if the patient died without intubation) <p>Key Secondary Endpoints:</p> <ul style="list-style-type: none"> Clinical worsening Discontinuation of supplemental oxygen among patients receiving it at baseline 	<p>Number of Participants:</p> <ul style="list-style-type: none"> mITT analysis: Tocilizumab (n = 161) and placebo (n = 81) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> Median age was 59.8 years (range 21.7–85.4 years). 58% of participants were men. 45% of participants were Hispanic or Latinx. 50% of participants had BMI ≥30; 49% had HTN, and 31% had diabetes. 80% of participants were hospitalized in non-ICU wards and receiving supplemental oxygen ≤6 L/min; 4% received high-flow oxygen; 16% required no supplemental oxygen. Median time from symptom onset to randomization was 9 days. Percentage of participants receiving concomitant medications: <ul style="list-style-type: none"> Glucocorticoids: 11% in tocilizumab arm vs. 6% in placebo arm RDV: 33% in tocilizumab arm vs. 29% in placebo arm. <p>Primary Outcomes:</p> <ul style="list-style-type: none"> There was no evidence of a treatment difference (i.e., time to intubation or death) between tocilizumab and placebo (HR 0.83; 95% CI, 0.38–1.81; <i>P</i> = 0.64). By Day 28, 11% of the patients in the tocilizumab arm vs. 13% in the placebo arm had been intubated or had died. <p>Key Secondary Outcomes:</p> <ul style="list-style-type: none"> By Day 28, 19% of patients in the tocilizumab arm vs. 17% in the placebo arm had experienced worsening of disease (HR 1.11; 95% CI, 0.59–2.10). The median time to discontinuation of oxygen was 5.0 days in the tocilizumab arm vs. 4.9 days in placebo arm (<i>P</i> = 0.69). Fewer serious infections occurred among participants in the tocilizumab arm than in the placebo arm (8.1% vs. 17.3%; <i>P</i> = 0.03). 	<p>Limitations:</p> <ul style="list-style-type: none"> The relatively small sample size and low event rates resulted in wide confidence intervals for primary and secondary outcomes. Some patients received RDV, and a few patients received steroids. <p>Interpretation:</p> <ul style="list-style-type: none"> In this study population, tocilizumab provided no benefit in preventing intubation or death (the primary outcome) or reducing the risk of clinical worsening or time to discontinuation of supplemental oxygen (secondary outcomes).

Study Design	Methods	Results	Limitations and Interpretation
Effect of Tocilizumab Versus Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia (CORIMUNO-TOCI-1)⁷			
<p>Open-label, randomized clinical trial in hospitalized patients with COVID-19 in France (n = 131)</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • COVID-19 confirmed by positive PCR test and/or findings/ abnormalities typical of COVID-19 on chest CT • Severe disease/pneumonia, requiring ≥ 3 L oxygen <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Receipt of high-flow oxygen or mechanical ventilation <p>Interventions</p> <p><i>1:1 Randomization:</i></p> <ul style="list-style-type: none"> • Single dose of tocilizumab 8 mg/kg on Day 1, possible second, fixed dose of tocilizumab 400 mg on Day 3 per provider if oxygen requirement not decreased by >50%, plus usual care, <i>or</i> • Usual care <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Scores >5 on the 10-point WHO Clinical Progression Scale on Day 4 • Survival without need of ventilation (including noninvasive ventilation) at Day 14 <p>Key Secondary Endpoint:</p> <ul style="list-style-type: none"> • Overall survival by Day 28 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • ITT analysis (n = 130): Tocilizumab (n = 63) and placebo (n = 67) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Median age was 64 years. • 68% of the participants were men. • Diagnosis of COVID-19 was confirmed by PCR test in 90% of participants. • Median time from symptom onset to randomization: 10 days • Baseline corticosteroids use was balanced (received by approximately 17% of participants in each arm) at randomization, but post randomization, more participants received corticosteroids in the control group (55%) than in the tocilizumab group (30%). <p>Primary Outcome:</p> <ul style="list-style-type: none"> • In the Bayesian analyses, evidence for the superiority of tocilizumab vs. usual care did not reach the prespecified threshold for the proportion of patients who died or needed high-flow oxygen, noninvasive ventilation, or IMV by Day 4 (19% of patients in tocilizumab arm vs. 28% in usual care arm), but did reach the threshold by Day 14 (24% of patients in tocilizumab arm vs. 36% in usual care arm (HR 0.58; 90% CrI, 0.33–1.00). <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> • There was no difference in overall survival by Day 28 between tocilizumab arm and usual care arm (89% vs. 88%; adjusted HR 0.92; 95% CI, 0.33–2.53). • SAEs occurred in 20 patients (32%) in the tocilizumab arm and 29 patients (43%) in the usual care arm ($P = 0.21$). • There were fewer serious bacterial infections in the tocilizumab arm (2) than in the usual care arm (11). 	<p>Limitations:</p> <ul style="list-style-type: none"> • Not blinded • Underpowered • More patients received dexamethasone/corticosteroids in the usual care arm. <p>Interpretation:</p> <ul style="list-style-type: none"> • Among patients with severe COVID-19, tocilizumab led to improved ventilator-free survival at Day 14 suggesting possible benefit, but the clinical implications are unclear as there was no difference in survival for tocilizumab vs. usual care through Day 28.

Study Design	Methods	Results	Limitations and Interpretation
Effect of Tocilizumab Versus Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia (RCT-TCZ-C19)⁸			
<p>Open-label RCT in hospitalized patients with COVID-19 in Italy (n = 126)</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • COVID-19 pneumonia confirmed by positive PCR test • Acute respiratory failure (i.e., PaO₂/FiO₂ 200–300 mm Hg), fever, and/or a CRP ≥10 mg/dL and/or CRP level increased to at least twice admission value <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Advanced age, multiple comorbidities, or any other condition precluding ICU-level care <p>Interventions</p> <p><i>1:1 Randomization:</i></p> <ul style="list-style-type: none"> • 2 doses of tocilizumab 8 mg/kg (maximum of 800 mg, second dose after 12 hours), or • Usual care <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Composite outcome defined as entry into ICU with IMV, death from all-causes, or clinical aggravation (PaO₂/FiO₂ <150 mm Hg) within 14 days <p>Key Secondary Endpoint:</p> <ul style="list-style-type: none"> • Mortality at 30 days 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • ITT analysis (n = 123): Tocilizumab (n = 60) and usual care (n = 63) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Median age was 60 years. • 61% of participants were men. • Participants in usual care arm had lower CRP, IL-6, ferritin, and D-dimer levels and received more antivirals than participants in tocilizumab arm. <p>Primary Outcome:</p> <ul style="list-style-type: none"> • No difference in the composite primary outcome of entry into ICU with mechanical ventilation, all-cause death, or clinical deterioration (PaO₂/FiO₂ <150 mm Hg) within 14 days: Met by 17 participants (28.3%) in tocilizumab arm vs. 17 (27.0%) in usual care arm (rate ratio 1.05; 95% CI, 0.59–1.86; P = 0.87) • ICU admissions: 10.0% of participants in tocilizumab arm vs. 7.9% in usual care arm (rate ratio 1.26; 95% CI, 0.41–3.91) • Mortality at 14 days: 1.7% in tocilizumab arm vs. 1.6% in usual care arm (rate ratio 1.05; 95% CI, 0.07–16.4) <p>Key Secondary Outcomes:</p> <ul style="list-style-type: none"> • There was no difference in mortality at 30 days between tocilizumab arm (3.3%) and usual care arm (1.6%; rate ratio 2.10; 95% CI, 0.20–22.6). • There were more AEs among the participants in tocilizumab arm (23.3%) than among those in usual care arm (11.1%). The reported AEs were mostly elevated ALT levels and reduced neutrophil counts. 	<p>Limitations:</p> <ul style="list-style-type: none"> • Not blinded • Small sample size • Mortality rate in the study population was significantly lower (2.4%) than in the general population in Italy (13.2%).⁹ • Because 14 patients in the control group (22%) received tocilizumab after they reached the primary endpoint, mortality outcomes are difficult to interpret. • There were some differences between the arms in baseline participant characteristics, including higher inflammatory markers in the tocilizumab arm. <p>Interpretation:</p> <ul style="list-style-type: none"> • This study demonstrated no evidence for a benefit of tocilizumab in patients hospitalized with COVID-19 pneumonia.

Study Design	Methods	Results	Limitations and Interpretation
Sarilumab in Hospitalized Patients With Severe or Critical COVID-19¹⁰			
<p>Multinational, double-blind, placebo-controlled, Phase 3 randomized trial in patients hospitalized with COVID-19 (n = 420)</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged ≥18 years • Laboratory-confirmed COVID-19 and clinical or radiographic evidence of pneumonia • Severe or critical disease (i.e., receiving supplemental oxygen, including delivery by nasal cannula or high-flow device, noninvasive ventilation or invasive ventilation, or treatment in ICU) <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Low probability of surviving or remaining at investigational site beyond 48 hours • Dysfunction of ≥2 organ systems, or need for ECMO or renal replacement therapy at screening <p>Interventions</p> <p><i>2:2:1 Randomization:</i></p> <ul style="list-style-type: none"> • Sarilumab IV 400 mg, <i>or</i> • Sarilumab IV 200 mg, <i>or</i> • Placebo <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Time from baseline to ≥2-point improvement in clinical status on a 7-point ordinal scale <p>Key Secondary Endpoint:</p> <ul style="list-style-type: none"> • Proportion of patients alive at Day 29 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • mITT analysis (n = 416): Sarilumab 400 mg (n = 173), sarilumab 200 mg (n = 159), and placebo (n = 84) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Median age was 59 years. • 63% of participants were men. • 77% of participants were White and 36% were Hispanic or Latino. • 42% of participants had BMI ≥30. • 43% of participants had HTN and 26% had type 2 diabetes. • 61% of participants had severe disease and 39% had critical disease. • 20% of participants received systemic corticosteroids before receiving their assigned intervention. <p>Primary Outcome:</p> <ul style="list-style-type: none"> • There was no difference in the median time to ≥2-point improvement in clinical status from baseline on the 7-point ordinal scale for either dose of sarilumab compared to placebo: <ul style="list-style-type: none"> • 12 days for placebo vs. 10 days for sarilumab 200 mg (HR 1.03; 95% CI, 0.75–1.40) and 10 days for sarilumab 400 mg (HR 1.14; 95% CI, 0.84–1.54). <p>Key Secondary Outcome:</p> <ul style="list-style-type: none"> • There was no difference among the arms in proportion of patients who were alive at Day 29 (92% in placebo arm, 90% in sarilumab 200 mg arm, 92% in sarilumab 400 mg arm). 	<p>Limitations:</p> <ul style="list-style-type: none"> • Low rate of baseline corticosteroid use and varying rate of overall corticosteroid use during the study • Moderate sample size with few participants in placebo arm <p>Interpretation:</p> <ul style="list-style-type: none"> • In hospitalized adults with severe or critical COVID-19, there was no benefit of sarilumab with respect to time to clinical improvement or mortality.

Study Design	Methods	Results	Limitations and Interpretation
Tocilizumab Plus Standard Care Versus Standard Care in Patients With Moderate to Severe COVID-19-Associated Cytokine Release Syndrome (COVINTOC)¹¹			
<p>Open-label, Phase 3 RCT in patients hospitalized with moderate to severe COVID-19 cytokine release syndrome in India</p>	<p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aged ≥18 years • SARS-CoV-2 infection confirmed by PCR test • Moderate disease (defined by respiratory rate 15–30 breaths/min, SpO₂ 90% to 94%) to severe disease (defined by respiratory rate ≥30 breaths/min, SpO₂ <90% on ambient air, ARDS, or septic shock) <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> • Low probability of surviving beyond 24 hours • Receipt of immunomodulatory drugs within previous 6 months • Serious medical conditions per judgment of investigators <p>Interventions</p> <p><i>1:1 Randomization:</i></p> <ul style="list-style-type: none"> • Tocilizumab 6 mg/kg (maximum dose 480 mg), second dose allowable if no improvement or worsening of clinical symptoms in next 7 days, <i>or</i> • Usual care <p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Proportion of patients with progression from moderate to severe disease or from severe disease to death by Day 14 <p>Key Secondary Endpoints:</p> <ul style="list-style-type: none"> • Incidence of mechanical ventilation • Ventilator-free days 	<p>Number of Participants:</p> <ul style="list-style-type: none"> • mITT analysis (n = 179): Tocilizumab (n = 91) and usual care (n = 88) <p>Participant Characteristics:</p> <ul style="list-style-type: none"> • Median age was 55 years. • 85% of participants were men. • The mean BMI was 27. • Approximately 40% of participants had HTN and 41% had type 2 diabetes. • In the tocilizumab arm, 45% of participants had moderate disease and 55% had severe disease. In the usual care arm, 53% of participants had moderate disease and 47% had severe disease. • 91% of participants received systemic corticosteroids during the study. <p>Primary Outcome:</p> <ul style="list-style-type: none"> • Overall, the percentage of patients with disease progression was 12.1% in tocilizumab arm and 18.2% in usual care arm. <p>Key Secondary Outcomes:</p> <ul style="list-style-type: none"> • There was no observed difference between the arms in incidence of mechanical ventilation or number of ventilator-free days. • In post hoc analysis, the percentage of patients who had progressed from severe COVID-19 to death was 16% in tocilizumab arm and 34% in usual care arm (<i>P</i> = 0.04). 	<p>Limitations:</p> <ul style="list-style-type: none"> • Open-label study • Underpowered • Lower dose of tocilizumab than in other trials <p>Interpretation:</p> <ul style="list-style-type: none"> • There was no demonstrated benefit of tocilizumab in hospitalized adults with moderate to severe COVID-19.

Key: AE = adverse event; ALT = alanine transaminase; ARDS = acute respiratory distress syndrome; AST = aspartate aminotransferase; BMI = body mass index; BACC = Boston Area COVID-19 Consortium; CRP = C-reactive protein; CT = computed tomography; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; EMPACTA = Evaluating Minority Patients With Actemra; HFNC = high-flow nasal cannula; HTN = hypertension; ICU = intensive care unit; IgM = immunoglobulin M; IL-6 = interleukin 6; IMV = invasive mechanical ventilation; ITT = intention to treat; IV = intravenous; LDH = lactate dehydrogenase; mITT = modified intention to treat; NIPPV = noninvasive positive-pressure ventilation; the Panel = the COVID-19 Treatment Guidelines Panel; PaO₂/FiO₂ = ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; PCR = polymerase chain reaction; RCT = randomized controlled trial; RDV = remdesivir; RECOVERY = Randomized Evaluation of COVID-19 Therapy; REMAP-CAP = Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia; SAE = serious adverse event; SOC = standard of care; SpO₂ = saturation of oxygen; TB = tuberculosis; ULN = upper limit of normal; WHO = World Health Organization

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

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Janus Kinase Inhibitors

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

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

Recommendations

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

Rationale

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

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

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

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

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

Monitoring, Adverse Effects, and Drug-Drug Interactions

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

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

The ACTT-2 study evaluated oral baricitinib 4 mg once daily;⁵ however, the standard dosage of baricitinib for FDA-approved indications is 2 mg once daily. Baricitinib use is not recommended in patients with impaired hepatic or renal function (estimated GFR < 60 mL/min/1.73 m²).⁷ There are limited clinical data on the use of baricitinib in combination with strong organic anion transporter 3 inhibitors, and, in general, coadministration is not advised.^{7,8}

Considerations in Pregnancy

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

Considerations in Children

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

Baricitinib

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

Clinical Data for COVID-19

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

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

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

Clinical Trials

Please check [ClinicalTrials.gov](https://www.clinicaltrials.gov) for the latest information on studies of baricitinib and COVID-19.

Ruxolitinib

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

Clinical Data for COVID-19

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

Clinical Trials

Please check [ClinicalTrials.gov](https://www.clinicaltrials.gov) for the latest information on studies of ruxolitinib and COVID-19.

Tofacitinib

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

Clinical Data for COVID-19

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

Considerations in Pregnancy

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

Clinical Trials

Please check [ClinicalTrials.gov](https://www.clinicaltrials.gov) for the latest information on studies of tofacitinib and COVID-19.

Bruton's Tyrosine Kinase Inhibitors

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

Recommendation

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

Acalabrutinib

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

Clinical Data for COVID-19

Data regarding acalabrutinib are limited to the results from a retrospective case series of 19 patients with severe COVID-19.²¹ Evaluation of the data to discern any clinical benefit is limited by the study's small sample size and lack of a control group.

Clinical Trials

Please check [ClinicalTrials.gov](https://www.clinicaltrials.gov) for the latest information on studies of acalabrutinib and COVID-19.

Ibrutinib

Ibrutinib is a first-generation BTK inhibitor that is FDA approved to treat various B-cell malignancies²² and to prevent chronic graft-versus-host disease in stem cell transplant recipients.²³ Based on results from a small case series, ibrutinib has been theorized to reduce inflammation and protect against ensuing lung injury in patients with COVID-19.²⁴

Clinical Data for COVID-19

Data regarding ibrutinib are limited to those from an uncontrolled, retrospective case series of six patients with COVID-19 who were receiving the drug for a condition other than COVID-19.²⁴ Evaluation of the data for any clinical benefit is limited by the series' small sample size and lack of a control group.

Clinical Trials

Please check [ClinicalTrials.gov](https://www.clinicaltrials.gov) for the latest information on studies of ibrutinib and COVID-19.

Zanubrutinib

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

Clinical Data for COVID-19

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

Clinical Trials

Please check [ClinicalTrials.gov](https://www.clinicaltrials.gov) for the latest information on studies of zanubrutinib and COVID-19.

Adverse Effects and Monitoring

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

Considerations in Pregnancy

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

Considerations in Children

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

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

Last Updated: April 21, 2021

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

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Colchicine					
Colchicine	Dose for COVID-19 in Clinical Trial <i>COLCORONA:</i> <ul style="list-style-type: none"> • Colchicine 0.5 mg twice daily for 3 days then once daily for 27 days 	<ul style="list-style-type: none"> • Diarrhea • Nausea • Vomiting • Cramping • Abdominal pain • Bloating • Loss of appetite • Neuromyotoxicity (rare)¹ • Blood dyscrasias (rare) 	<ul style="list-style-type: none"> • CBC • Renal function • Hepatic function 	<ul style="list-style-type: none"> • 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. 	<ul style="list-style-type: none"> • Colchicine should be avoided in patients with severe renal insufficiency, and those with moderate renal insufficiency should be monitored for AEs. • A list of clinical trials is available: Colchicine Availability: <ul style="list-style-type: none"> • COLCORONA used 0.5 mg tablets for dosing; in the United States, colchicine is available as 0.6 mg tablets.

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Corticosteroids					
Dexamethasone	Dose for COVID-19: <ul style="list-style-type: none"> Dexamethasone 6 mg IV or PO once daily, for up to 10 days or until hospital discharge, whichever comes first² 	<ul style="list-style-type: none"> Hyperglycemia Secondary infections Reactivation of latent infections (e.g., HBV, HSV, strongyloidiasis, TB) Psychiatric disturbances Avascular necrosis Adrenal insufficiency Increased blood pressure Peripheral edema Myopathy (particularly if used with neuromuscular blocking agents) 	<ul style="list-style-type: none"> Blood glucose Blood pressure Signs and symptoms of new infection When initiating dexamethasone, consider appropriate screening and treatment to reduce the risk of <i>Strongyloides</i> hyperinfection in patients at high risk of strongyloidiasis or fulminant reactivations of HBV.³⁻⁵ 	<ul style="list-style-type: none"> Moderate CYP3A4 inducer CYP3A4 substrate Although coadministration of RDV and dexamethasone has not been formally studied, a clinically significant PK interaction is not predicted (Gilead, written communication, August 2020). 	<ul style="list-style-type: none"> If dexamethasone is not available, an alternative corticosteroid (e.g., prednisone, methylprednisolone, hydrocortisone) can be used. The approximate total daily dose equivalencies for these glucocorticoids to dexamethasone 6 mg (PO or IV) are: prednisone 40 mg, methylprednisolone 32 mg, and hydrocortisone 160 mg. A list of clinical trials is available: Dexamethasone
Fluvoxamine					
Fluvoxamine	Dose for COVID-19 in Clinical Trials: <ul style="list-style-type: none"> Various dosing regimens used 	<ul style="list-style-type: none"> Nausea Diarrhea Dyspepsia Asthenia Insomnia Somnolence Sweating Suicidal ideation (rare) 	<ul style="list-style-type: none"> Assess for drug interactions. Hepatic function Monitor for withdrawal symptoms when tapering dose. 	<ul style="list-style-type: none"> Fluvoxamine is a CYP2D6 substrate. Fluvoxamine inhibits several CYP450 isoenzymes (CYP1A2, CYP2C9, CYP3A4, CYP2C19, CYP2D6). Coadministration of tizanidine, thioridazine, alosetron, or pimozide with fluvoxamine is contraindicated. 	<ul style="list-style-type: none"> 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.

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Fluvoxamine , continued					
					<ul style="list-style-type: none"> A list of clinical trials is available: Fluvoxamine
Interferons					
Interferon Alfa	<p>Peg-IFN Alfa-2a <i>Dose for MERS:</i></p> <ul style="list-style-type: none"> Peg-IFN alfa-2a 180 µg SQ once weekly for 2 weeks^{6,7} <p>IFN Alfa-2b <i>Dose for COVID-19 in Clinical Trials:</i></p> <ul style="list-style-type: none"> Nebulized IFN alfa-2b 5 million international units twice daily (no duration listed in the study methods)⁸ 	<ul style="list-style-type: none"> Flu-like symptoms (e.g., fever, fatigue, myalgia)⁹ Injection site reactions Liver function abnormalities Decreased blood counts Worsening depression Insomnia Irritability Nausea Vomiting HTN Induction of autoimmunity 	<ul style="list-style-type: none"> CBC with differential Liver enzymes; avoid if Child-Pugh Score >6 Depression, psychiatric symptoms Reduce dose in patients with CrCl <30 mL/min. 	<ul style="list-style-type: none"> Low potential for drug-drug interactions Inhibition of CYP1A2 	<ul style="list-style-type: none"> For COVID-19, IFN alfa has primarily been used as nebulization and usually as part of a combination regimen. Use with caution with other hepatotoxic agents. Reduce dose if ALT >5 times ULN; discontinue if bilirubin level also increases. Reduce dose or discontinue if neutropenia or thrombocytopenia occur. A list of clinical trials is available: Interferon <p>Availability:</p> <ul style="list-style-type: none"> Neither nebulized IFN alfa-2b nor IFN alfa-1b are FDA-approved for use in the United States.

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Interferons, continued					
Interferon Beta	IFN Beta-1a <i>Dose for MERS:</i> <ul style="list-style-type: none"> • IFN beta-1a 44 mcg SQ 3 times weekly⁷ <i>Dose for COVID-19:</i> <ul style="list-style-type: none"> • Dose and duration unknown IFN Beta-1b <i>Dose for COVID-19:</i> <ul style="list-style-type: none"> • IFN beta-1b 8 million international units SQ every other day, up to 7 days total¹⁰ 	<ul style="list-style-type: none"> • Flu-like symptoms (e.g., fever, fatigue, myalgia)¹¹ • Leukopenia, neutropenia, thrombocytopenia, lymphopenia • Liver function abnormalities (ALT > AST) • Injection site reactions • Headache • Hypertonia • Pain • Rash • Worsening depression • Induction of autoimmunity 	<ul style="list-style-type: none"> • Liver enzymes • CBC with differential • Worsening CHF • Depression, suicidal ideation 	<ul style="list-style-type: none"> • Low potential for drug-drug interactions 	<ul style="list-style-type: none"> • Use with caution with other hepatotoxic agents. • Reduce dose if ALT >5 times ULN. • A list of clinical trials is available: Interferon Availability: <ul style="list-style-type: none"> • Several products are available in the United States; product doses differ. <i>IFN Beta-1a Products:</i> <ul style="list-style-type: none"> • Avonex, Rebif <i>IFN Beta-1b Products:</i> <ul style="list-style-type: none"> • Betaseron, Extavia

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Interleukin-1 Inhibitor					
Anakinra	<p>Dose for Rheumatoid Arthritis:</p> <ul style="list-style-type: none"> Anakinra 100 mg SQ once daily <p>Dose for COVID-19:</p> <ul style="list-style-type: none"> Dose and duration vary by study Has also been used as IV infusion 	<ul style="list-style-type: none"> Neutropenia (particularly with concomitant use of other agents that can cause neutropenia) Anaphylaxis Headache Nausea Diarrhea Sinusitis Arthralgia Flu-like symptoms Abdominal pain Injection site reactions Liver enzyme elevations 	<ul style="list-style-type: none"> CBC with differential Renal function (reduce dose in patients with CrCl <30 mL/min) Liver enzymes 	<ul style="list-style-type: none"> Use with TNF-blocking agents is not recommended due to increased risk of infection. 	<ul style="list-style-type: none"> A list of clinical trials is available: Anakinra
Interleukin-6 Inhibitors					
<i>Anti-Interleukin-6 Receptor Monoclonal Antibodies</i>					
Sarilumab¹²	<p>Dose for COVID-19 in Clinical Trial (See ClinicalTrials.gov Identifier NCT04315298):</p> <ul style="list-style-type: none"> Sarilumab 400 mg IV (single dose)¹³ 	<ul style="list-style-type: none"> Neutropenia, thrombocytopenia GI perforation HSR Increased liver enzymes HBV reactivation Infusion-related reaction 	<ul style="list-style-type: none"> Monitor for HSR. Monitor for infusion reactions. Neutrophils Platelets Liver enzymes 	<ul style="list-style-type: none"> Elevated IL-6 may downregulate CYP enzymes; use of sarilumab may lead to increased metabolism of drugs that are CYP450 substrates. Effects on CYP450 may persist for weeks after therapy. 	<ul style="list-style-type: none"> Treatment with sarilumab may mask signs of acute inflammation or infection (i.e., by suppressing fever and CRP levels). A list of clinical trials is available: Sarilumab <p>Availability:</p> <ul style="list-style-type: none"> Sarilumab for IV administration is not an approved formulation in the United States.

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Interleukin-6 Inhibitors , continued					
<i>Anti-Interleukin-6 Receptor Monoclonal Antibodies</i> , continued					
Tocilizumab¹⁴	Dose for COVID-19 in Clinical Trial: <ul style="list-style-type: none"> • Single dose of tocilizumab 8 mg/kg actual body weight IV • Dose should not exceed tocilizumab 800 mg. • Administer in combination with dexamethasone. • In clinical trials, some patients received a second dose of tocilizumab at the discretion of treating physicians; however, there are insufficient data to determine which patients, if any, would benefit from an additional dose of the drug. 	<ul style="list-style-type: none"> • Infusion-related reaction • HSR • GI perforation • Hepatotoxicity • Treatment-related changes on laboratory tests for neutrophils, platelets, lipids, and liver enzymes • HBV reactivation 	<ul style="list-style-type: none"> • Monitor for HSR. • Monitor for infusion reactions. • Neutrophils • Platelets • Liver enzymes • Cases of severe and disseminated strongyloidiasis have been reported with the use of tocilizumab and corticosteroids in patients with COVID-19.^{15,16} Prophylactic treatment with ivermectin should be considered for persons who are from areas where strongyloidiasis is endemic.³ 	<ul style="list-style-type: none"> • Elevated IL-6 may downregulate CYP enzymes; use of tocilizumab may lead to increased metabolism of drugs that are CYP450 substrates. • Effects on CYP450 may persist for weeks after therapy. 	<ul style="list-style-type: none"> • Tocilizumab use should be avoided in patients who are significantly immunocompromised. The safety of using tocilizumab plus a corticosteroid in immunocompromised patients is unknown. • May mask signs of acute inflammation or infection (i.e., by suppressing fever and CRP levels). • The SQ formulation of tocilizumab is not intended for IV administration. • A list of clinical trials is available: Tocilizumab

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Interleukin-6 Inhibitors , continued					
<i>Anti-Interleukin-6 Monoclonal Antibody</i>					
Siltuximab	Dose for Multicentric Castleman Disease: <ul style="list-style-type: none"> Siltuximab 11 mg/kg administered over 1 hour by IV infusion every 3 weeks¹⁷ Dose for COVID-19: <ul style="list-style-type: none"> Dose and duration unknown 	<ul style="list-style-type: none"> Infusion-related reaction HSR GI perforation Neutropenia HTN Dizziness Rash Pruritus Hyperuricemia 	<ul style="list-style-type: none"> Monitor for HSR. Monitor for infusion reactions. Neutrophils 	<ul style="list-style-type: none"> Elevated IL-6 may downregulate CYP enzymes; use of siltuximab may lead to increased metabolism of drugs that are CYP450 substrates. Effects on CYP450 may persist for weeks after therapy. 	<ul style="list-style-type: none"> May mask signs of acute inflammation or infection (i.e., by suppressing fever and CRP levels). A list of clinical trials is available: Siltuximab
Kinase Inhibitors					
<i>Bruton's Tyrosine Kinase Inhibitors</i>					
Acalabrutinib	Dose for FDA-Approved Indications: <ul style="list-style-type: none"> Acalabrutinib 100 mg PO every 12 hours Dose for COVID-19: <ul style="list-style-type: none"> Dose and duration unknown 	<ul style="list-style-type: none"> Hemorrhage Cytopenias (neutropenia, anemia, thrombocytopenia, lymphopenia) Atrial fibrillation and flutter Infection Headache Diarrhea Fatigue Myalgia 	<ul style="list-style-type: none"> CBC with differential Signs and symptoms of bleeding (particularly when coadministered with anticoagulant or antiplatelet therapy) Monitor for cardiac arrhythmias. Monitor for new infections. 	<ul style="list-style-type: none"> Avoid concomitant use with strong CYP3A inhibitors or inducers. Dose reduction may be necessary with moderate CYP3A4 inhibitors. Avoid concomitant PPI use. H2-receptor antagonist should be administered 2 hours after acalabrutinib. 	<ul style="list-style-type: none"> Avoid use in patients with severe hepatic impairment. Patients with underlying cardiac risk factors, hypertension, or acute infections may be predisposed to atrial fibrillation. A list of clinical trials is available: Acalabrutinib

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Kinase Inhibitors, continued					
<i>Bruton's Tyrosine Kinase Inhibitors, continued</i>					
Ibrutinib	<p>Dose for FDA-Approved Indications:</p> <ul style="list-style-type: none"> Ibrutinib 420 mg or 560 mg PO once daily <p>Dose for COVID-19:</p> <ul style="list-style-type: none"> Dose and duration unknown 	<ul style="list-style-type: none"> Hemorrhage Cardiac arrhythmias Serious infections Cytopenias (thrombocytopenia, neutropenia, anemia) HTN Diarrhea Musculoskeletal pain Rash 	<ul style="list-style-type: none"> CBC with differential Blood pressure Signs and symptoms of bleeding (particularly when coadministered with anticoagulant or antiplatelet therapy) Monitor for cardiac arrhythmias. Monitor for new infections. 	<ul style="list-style-type: none"> Avoid concomitant use with strong CYP3A inhibitors or inducers. Dose reduction may be necessary with moderate CYP3A4 inhibitors. 	<ul style="list-style-type: none"> Avoid use in patients with severe baseline hepatic impairment. Dose modifications required in patients with mild or moderate hepatic impairment. Patients with underlying cardiac risk factors, HTN, or acute infections may be predisposed to cardiac arrhythmias. A list of clinical trials is available: Ibrutinib
Zanubrutinib	<p>Dose for FDA-Approved Indications:</p> <ul style="list-style-type: none"> Zanubrutinib 160 mg PO twice daily or 320 mg PO once daily <p>Dose for COVID-19:</p> <ul style="list-style-type: none"> Dose and duration unknown 	<ul style="list-style-type: none"> Hemorrhage Cytopenias (neutropenia, thrombocytopenia, anemia, leukopenia) Atrial fibrillation and flutter Infection Rash Bruising Diarrhea Cough Musculoskeletal pain 	<ul style="list-style-type: none"> CBC with differential Signs and symptoms of bleeding Monitor for cardiac arrhythmias. Monitor for new infections. 	<ul style="list-style-type: none"> Avoid concomitant use with moderate or strong CYP3A inducers. Dose reduction required with moderate and strong CYP3A4 inhibitors. 	<ul style="list-style-type: none"> Dose reduction required in patients with severe hepatic impairment. A list of clinical trials is available: Zanubrutinib

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Janus Kinase Inhibitors					
Baricitinib¹⁸	Dose for Rheumatoid Arthritis: <i>Adults:</i> <ul style="list-style-type: none"> • Baricitinib 2 mg PO once daily Dose for COVID-19:¹⁹ <i>Adults:</i> <ul style="list-style-type: none"> • Baricitinib 4 mg PO once daily for 14 days or until hospital discharge <i>Children:</i> <ul style="list-style-type: none"> • Limited data are available. Dose per the FDA EUA: <ul style="list-style-type: none"> • Aged ≥9 years: Baricitinib 4 mg PO once daily for 14 days or until hospital discharge • Aged ≥2 years to <9 years: Baricitinib 2 mg PO once daily for 14 days or until hospital discharge • See full prescribing information for dosing recommendations in patients with renal or hepatic impairment.¹⁸ 	<ul style="list-style-type: none"> • Lymphoma and other malignancies • Thrombosis • GI perforation • Treatment-related changes in lymphocytes, neutrophils, Hgb, liver enzymes • HSV reactivation • Herpes zoster 	<ul style="list-style-type: none"> • CBC with differential • Renal function • Liver enzymes • Monitor for new infections. 	<ul style="list-style-type: none"> • Dose modification is recommended when concurrently administering a strong OAT3 inhibitor. • Avoid concomitant administration of live vaccines. 	<ul style="list-style-type: none"> • Baricitinib is not recommended for patients with severe hepatic or renal impairment. • A list of clinical trials is available: Baricitinib Availability: <ul style="list-style-type: none"> • Baricitinib is available through an FDA EUA. The EUA allows for the use of baricitinib, in combination with RDV, for the treatment of COVID-19 for hospitalized adults and pediatric patients aged ≥2 years who require supplemental oxygen, IMV, or ECMO.¹⁹

Drug Name	Dosing Regimen <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Janus Kinase Inhibitors, continued					
Ruxolitinib	Dose for FDA-Approved Indications: <ul style="list-style-type: none"> Ruxolitinib 5 mg–20 mg PO twice daily Dose for COVID-19 in Clinical Trials: <ul style="list-style-type: none"> Ruxolitinib 5 mg–20 mg PO twice daily, for 14 days 	<ul style="list-style-type: none"> Thrombocytopenia Anemia Neutropenia Liver enzyme elevations Risk of infection Dizziness Headache Diarrhea CPK elevation Herpes zoster 	<ul style="list-style-type: none"> CBC with differential Liver enzymes Monitor for new infections. 	<ul style="list-style-type: none"> Dose modifications required when administered with strong CYP3A4 inhibitors. Avoid use with doses of fluconazole >200 mg. 	<ul style="list-style-type: none"> 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 FDA-Approved Indications: <ul style="list-style-type: none"> Tofacitinib 5 mg PO twice daily for rheumatoid and psoriatic arthritis Tofacitinib 10 mg PO twice daily for ulcerative colitis Dose for COVID-19: <ul style="list-style-type: none"> Dose and duration unknown; a planned COVID-19 clinical trial will evaluate tofacitinib 10 mg twice daily for 14 days. 	<ul style="list-style-type: none"> Thrombotic events (pulmonary embolism, DVT, arterial thrombosis) Anemia Risk of infection GI perforation Diarrhea Headache Herpes zoster Lipid elevations Liver enzyme elevations Lymphoma and other malignancies 	<ul style="list-style-type: none"> CBC with differential Liver enzymes Monitor for new infections. 	<ul style="list-style-type: none"> 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. Avoid administration of live vaccines. 	<ul style="list-style-type: none"> Avoid use in patients with ALC <500 cells/mm³, ANC <1,000 cells/mm³, 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 <i>There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.</i>	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Non-SARS-CoV-2 Specific Immunoglobulin					
Non-SARS-CoV-2 Specific Immunoglobulin	<ul style="list-style-type: none"> • Dose varies based on indication and formulation. 	<ul style="list-style-type: none"> • 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. 	<ul style="list-style-type: none"> • Monitor for transfusion-related reactions. • Monitor vital signs at baseline and during and after infusion. • Discontinue if renal function deteriorates during treatment. 	<ul style="list-style-type: none"> • IVIG may interfere with immune response to certain vaccines. 	<ul style="list-style-type: none"> • 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; CBC = complete blood count; CHF = congestive heart failure; COLCORONA = Colchicine Coronavirus SARS-CoV2 Trial; CPK = creatine phosphokinase; CrCl = creatinine clearance; CRP = C-reactive protein; CYP = cytochrome P; DVT = deep vein thrombosis; ECMO = extracorporeal membrane oxygenation; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; GI = gastrointestinal; HBV = hepatitis B; Hgb = hemoglobin; HSR = hypersensitivity reaction; HSV = herpes simplex virus; HTN = hypertension; IFN = interferon; IL = interleukin; IMV = invasive mechanical ventilation; IV = intravenous; IVIG = intravenous immunoglobulin; MAOI = monoamine oxidase inhibitor; MERS = Middle East respiratory syndrome; OAT = organic anion transporter; the Panel = the COVID-19 Treatment Guidelines Panel; Peg-IFN = pegylated interferon; P-gp= P-glycoprotein; PK = pharmacokinetic; PO = orally; PPI = proton pump inhibitor; RDV = remdesivir; SQ = subcutaneous; TB = tuberculosis; TNF = tumor necrosis factor; TRALI = transfusion-related acute lung injury; ULN = upper limit of normal

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Antithrombotic Therapy in Patients with COVID-19

Last Updated: February 11, 2021

Summary Recommendations

Laboratory Testing

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

Chronic Anticoagulant and Antiplatelet Therapy

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

Venous Thromboembolism Prophylaxis and Screening

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

Hospitalized Children With COVID-19

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

Treatment

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

Special Considerations During Pregnancy and Lactation

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

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

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

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

Association Between COVID-19 and Thromboembolism

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

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

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

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

hospitalized COVID-19 patients from a single center in the United States reported in-hospital mortality in 22.5% of patients who received therapeutic anticoagulation and 22.8% of patients who did not receive anticoagulation. The study further reported that in a subset of 395 mechanically ventilated patients, 29.1% of the patients who received anticoagulation and 62.7% of those who did not receive anticoagulation died. The study had important limitations: it lacked details on patient characteristics, indications for anticoagulant initiation, and descriptions of other therapies that the patients received that may have influenced mortality. In addition, the authors did not discuss the potential impact of survival bias on the study results. For these reasons, the data are not sufficient to influence standard of care, and this study further emphasizes the need for prospective trials to define the risks and potential benefits of therapeutic anticoagulation in patients with COVID-19.¹⁸ Three international trials (Antithrombotic Therapy to Ameliorate Complications of COVID-19 [ATTACC], Therapeutic Anticoagulation; Accelerating COVID-19 Therapeutic Interventions and Vaccines-4 [ACTIV-4], and the Randomized, Embedded, Multi-factorial Adaptive Platform Trial for Community-Acquired Pneumonia [REMAP-CAP]) compared the effectiveness of therapeutic dose anticoagulation and prophylactic dose anticoagulation in reducing the need for organ support over 21 days in moderately ill or critically ill adults hospitalized for COVID-19. The need for organ support was defined as requiring high-flow nasal oxygen, invasive or noninvasive mechanical ventilation, vasopressor therapy, or extracorporeal membrane oxygenation (ECMO). The trials paused enrollment of patients requiring intensive care unit (ICU)-level care after an interim pooled analysis demonstrated futility of therapeutic anticoagulation in improving organ support, and a concern for safety. The results of the interim analysis are available on the [ATTACC website](#). Unblinded data and additional study outcomes, including the occurrence of thrombosis, are expected to be reported soon.¹⁹

A small, single-center randomized trial (n = 20) compared therapeutic and prophylactic anticoagulation in mechanically ventilated patients with D-dimers >1,000 µg/L (as measured by the VIDAS D-dimer Exclusion II assay). Only the patients treated with therapeutic anticoagulation showed improvement in the ratio of arterial oxygen partial pressure of oxygen to fraction of inspired oxygen (PaO₂/FiO₂). The number of ventilator-free days was higher in the therapeutic anticoagulation arm than in the prophylactic anticoagulation arm (15 days [IQR 6–16] vs. 0 days [IQR 0–11]; P = 0.028). There was no difference between the arms in in-hospital or 28-day mortality. Two patients treated with therapeutic anticoagulation had minor bleeding, and two patients in each arm experienced thrombosis.²⁰ Additional evidence from large, multicenter trials is needed, and the trial results are expected soon.

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

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

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

Monitoring Coagulation Markers in Patients With COVID-19

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

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

Managing Antithrombotic Therapy in Patients With COVID-19

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

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

Chronic Anticoagulant or Antiplatelet Therapy

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

Patients with COVID-19 Who Are Managed as Outpatients

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

Hospitalized Patients With COVID-19

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

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

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

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

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

Hospitalized Children With COVID-19

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

Patients With COVID-19 Who Are Discharged from the Hospital

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

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

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

Special Considerations During Pregnancy and Lactation

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

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

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

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

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

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

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

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Supplements

Last Updated: February 11, 2021

Summary Recommendations
<p>Vitamin C</p> <ul style="list-style-type: none">• There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of vitamin C for the treatment of COVID-19.
<p>Vitamin D</p> <ul style="list-style-type: none">• There are insufficient data for the Panel to recommend either for or against the use of vitamin D for the treatment of COVID-19.
<p>Zinc</p> <ul style="list-style-type: none">• There are insufficient data for the Panel to recommend either for or against the use of zinc for the treatment of COVID-19.• The Panel recommends against using zinc supplementation above the recommended dietary allowance for the prevention of COVID-19, except in a clinical trial (BIII).
<p>Rating of Recommendations: A = Strong; B = Moderate; C = Optional</p> <p>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</p>

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

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

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

Vitamin C

Last Updated: April 21, 2021

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

Recommendation for Non-Critically Ill Patients With COVID-19

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

Rationale

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

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

Rationale

There are no 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 [$\text{PaO}_2/\text{FiO}_2$]) 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 shock¹² 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](https://clinicaltrials.gov) for a list of clinical trials that are evaluating the use of vitamin C in patients with COVID-19.

Other Considerations

It is important to note that high circulating concentrations of vitamin C may affect the accuracy of point-of-care glucometers.^{16,17}

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Vitamin D

Last Updated: April 21, 2021

Recommendation

- There are insufficient data 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 adults³ 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](https://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 D3 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 D₃ 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 D₃ did not significantly reduce the length of stay for hospitalized patients with COVID-19.

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Zinc

Last Updated: April 21, 2021

Recommendations

- There are insufficient data 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](https://clinicaltrials.gov) for more information about ongoing studies). The recommended dietary allowance for elemental zinc is 11 mg daily for men and 8 mg for nonpregnant women.⁵ The doses used in registered clinical trials for patients with COVID-19 vary between studies, with a maximum dose of zinc sulfate 220 mg (50 mg of elemental zinc) twice daily. However, there are currently insufficient data to recommend either for or against the use of zinc for the treatment of COVID-19.

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

Clinical Data

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

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

Results

- There were no significant differences between the two arms in the percentages of patients who recovered within 28 days (79.2% in the hydroxychloroquine plus zinc arm vs. 77.9% in the hydroxychloroquine only arm; $P = 0.969$), the need for mechanical ventilation ($P = 0.537$), or

overall mortality ($P = 0.986$).

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

Limitations

- This study had a relatively small sample size.

Interpretation

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

Open-Label, Randomized Trial of Zinc Versus Ascorbic Acid Versus Zinc Plus Ascorbic Acid Versus Standard of Care in Outpatients With COVID-19

In an open-label clinical trial that was conducted at two sites in the United States, outpatients with laboratory-confirmed SARS-CoV-2 infection were randomized to receive either 10 days of zinc gluconate 50 mg, ascorbic acid 8,000 mg, both agents, or standard of care. The primary end point was the number of days required to reach a 50% reduction in the patient's symptom severity score. The study was stopped early by an operational and safety monitoring board due to futility after 40% of the planned 520 participants were enrolled ($n = 214$).⁹

Results

- Participants who received standard of care achieved a 50% reduction in their symptom severity scores at a mean of 6.7 days (SD 4.4 days) compared with 5.5 days (SD 3.7 days) for the ascorbic acid arm, 5.9 days (SD 4.9 days) for the zinc gluconate arm, and 5.5 days (SD 3.4 days) for the arm that received both agents (overall $P = 0.45$).
- Nonserious adverse effects occurred more frequently in patients who received supplements than in those who did not; 39.5% of patients in the ascorbic acid arm, 18.5% in the zinc gluconate arm, and 32.1% in the arm that received both agents experienced nonserious adverse effects compared with 0% of patients in the standard of care arm (overall $P < 0.001$). The most common nonserious adverse effects in this study were gastrointestinal events.

Limitations

- The study had a small sample size.
- There was no placebo control.

Interpretation

In outpatients with COVID-19, treatment with high-dose zinc gluconate, ascorbic acid, or a combination of the two supplements did not significantly decrease the number of days required to reach a 50% reduction in a symptom severity score compared with standard of care.

Observational Study of Zinc Supplementation in Hospitalized Patients

A retrospective study enrolled 242 patients with polymerase chain reaction-confirmed SARS-CoV-2 infection who were admitted to Hoboken University Medical Center. One hundred and ninety-six patients (81.0%) received a total daily dose of zinc sulfate 440 mg (100 mg of elemental zinc); of those, 191 patients (97%) also received hydroxychloroquine. Among the 46 patients who did not receive zinc, 32 patients (70%) received hydroxychloroquine. The primary outcome was days from hospital admission to in-hospital mortality, and the primary analysis explored the causal association between zinc therapy and survival.¹⁰

Results

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

Limitations

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

Interpretation

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

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

This study has not been peer reviewed.

This multicenter, retrospective cohort study of hospitalized adults with SARS-CoV-2 infection who were admitted to four New York City hospitals between March 10 and May 20, 2020, compared patients who received zinc plus hydroxychloroquine to those who received treatment that did not include this combination.¹¹

Results

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

Limitations

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

Interpretation

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

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Considerations for Certain Concomitant Medications in Patients with COVID-19

Last Updated: April 21, 2021

Summary Recommendations
<ul style="list-style-type: none">• Patients with COVID-19 who are receiving concomitant medications (e.g., angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], statins, systemic or inhaled corticosteroids, nonsteroidal anti-inflammatory drugs, acid-suppressive therapy) for underlying medical conditions should not discontinue these medications during acute management of COVID-19 unless discontinuation is otherwise warranted by their clinical condition (AIIa for ACE inhibitors and ARBs; AIII for other medications).• The COVID-19 Treatment Guidelines Panel recommends against using medications off-label to treat COVID-19 if they have not demonstrated safety and efficacy in patients with COVID-19, except in a clinical trial (AIII).
Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

Individuals with underlying medical conditions such as cardiovascular disease, pulmonary disease, diabetes, or malignancy are at higher risk of severe illness with COVID-19. These patients are often prescribed medications to treat their underlying medical conditions. It is unclear whether these concomitant medications have a positive or negative impact on the treatment and outcomes of COVID-19.

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

Patients with COVID-19 who are treated with concomitant medications for an underlying medical condition should not discontinue these medications during acute management of COVID-19 unless discontinuation is otherwise warranted by their clinical condition (**AIII**). Several commonly used medications have been proposed to have direct effects on SARS-CoV-2 or to impact the pathogenesis of COVID-19. This section will address considerations for using these medications as potential treatments for COVID-19 if data are available.

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

Recommendations

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

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

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

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

Overall, there was no difference between the arms in the primary endpoint of days alive and out of the hospital; the mean number of days alive and out of the hospital was 21.9 days in the discontinuation arm and 22.9 days in the continuation arm (mean ratio 0.95; 95% CI, 0.90–1.01). No differences were observed in the secondary endpoints of the percentages of patients who experienced death, cardiovascular events, or COVID-19 progression. Subgroup analyses identified an interaction between the treatment effect and the subgroup of patients with greater severity of COVID-19 (those with oxygen saturation <94%, pulmonary infiltrates >50%, or a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen [$\text{PaO}_2/\text{FiO}_2$] <300 mm Hg). There may be a clinical benefit to continuing ACE inhibitor therapy or ARB therapy in these patients. Because of limitations in the available data, it is difficult to interpret these findings in subsets of patients with certain comorbid conditions, severe or critical illness, and pre-existing diagnoses of heart failure.⁶

Additional investigations of the role of ACE inhibitors, ARBs, and recombinant human ACE2 in the management of COVID-19 are underway.¹ Please see [ClinicalTrials.gov](https://www.clinicaltrials.gov) for the latest information.

Corticosteroids

Recommendation

- Patients with COVID-19 who are receiving **inhaled or systemic corticosteroids** for an underlying condition should not discontinue these medications unless discontinuation is otherwise warranted by their clinical condition (**AIII**).

Systemic treatment with dexamethasone or other corticosteroids is recommended for certain populations of patients with COVID-19. See [Therapeutic Management of Adults With COVID-19](#), [Corticosteroids](#), and [Special Considerations in Pregnancy](#) for specific recommendations.

Oral corticosteroid therapy prescribed for an underlying medical condition (e.g., primary or secondary adrenal insufficiency, rheumatological diseases) should be continued in patients after the diagnosis of COVID-19.⁷ Supplemental or stress-dose steroids may be indicated in individual cases.

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

The use of corticosteroids has been associated with delayed viral clearance and/or worse clinical outcomes in patients with other viral respiratory infections.¹¹⁻¹³ Some studies have suggested that systemic corticosteroids slow SARS-CoV-2 clearance, especially when given earlier in the course of infection.¹⁴⁻¹⁸ There is insufficient evidence to identify a relationship between inhaled corticosteroid use and the speed of viral clearance.

HMG-CoA Reductase Inhibitors (Statins)

Recommendations

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

HMG-CoA reductase inhibitors, or statins, affect ACE2 as part of their function in reducing endothelial dysfunction. It has been proposed that these agents have a potential role in managing patients with severe COVID-19.¹⁹

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

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

Nonsteroidal Anti-Inflammatory Drugs

Recommendations

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

In March 2020, news agencies promoted reports that anti-inflammatory drugs may worsen COVID-19. It has been proposed that NSAIDs such as ibuprofen can increase the expression of ACE2² and inhibit antibody production.²³ Shortly after these reports, the Food and Drug Administration stated that there is no evidence linking the use of NSAIDs with worsening of COVID-19 and advised patients to use NSAIDs as directed.²⁴

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

Acid-Suppressive Therapy

Recommendations

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

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

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

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

Results from ongoing clinical trials will provide more insights into the role of famotidine in the treatment of COVID-19. Please see [ClinicalTrials.gov](https://www.clinicaltrials.gov) for the latest information.

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

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COVID-19 and Special Populations

Last Updated: October 9, 2020

Key Considerations

There is current guidance from the [Centers for Disease Control and Prevention \(CDC\)](#), the [American College of Obstetricians and Gynecologists \(ACOG\)](#), and the [Society for Maternal-Fetal Medicine \(SMFM\)](#) on the management of pregnant patients with COVID-19.¹⁻⁴ This section of the COVID-19 Treatment Guidelines complements that guidance. Below are key considerations regarding the management of COVID-19 in pregnancy.

- Pregnant women should be counseled about the potential for severe disease from SARS-CoV-2 infection and the recommended measures to take to protect themselves and their families from infection.
- If hospitalization for COVID-19 is indicated in a pregnant woman, care should be provided in a facility that can conduct maternal and fetal monitoring, when appropriate.
- Management of COVID-19 in the pregnant patient should include:
 - Fetal and uterine contraction monitoring, when appropriate, based on gestational age
 - Individualized delivery planning
 - A multispecialty, team-based approach that may include consultation with obstetric, maternal-fetal medicine, infectious disease, pulmonary and critical care, and pediatric specialists, as appropriate
- The COVID-19 Treatment Guidelines Panel (the Panel) recommends that potentially effective treatment for COVID-19 should not be withheld from pregnant women because of theoretical concerns related to the safety of therapeutic agents in pregnancy (**AIII**).
- Decisions regarding the use of drugs approved for other indications or investigational drugs for the treatment of COVID-19 in pregnant patients must be made with shared decision-making between the patient and the clinical team, considering the safety of the medication for the pregnant woman and the fetus and the severity of maternal disease. For detailed guidance on the use of COVID-19 therapeutic agents in pregnancy, please refer to the pregnancy considerations subsection of each individual section of the Guidelines.

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

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

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

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

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

Special Considerations in Pregnancy

Last Updated: August 27, 2020

Epidemiology of COVID-19 in Pregnancy

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

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

This analysis has a number of significant limitations, including:

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

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

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

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

- Fetal and uterine contraction monitoring, when appropriate, based on gestational age

- Individualized delivery planning
- A multispecialty, team-based approach that may include consultation with obstetric, maternal-fetal medicine, infectious disease, pulmonary and critical care, and pediatric specialists, as appropriate.

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

Timing of Delivery

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

Management of COVID-19 in the Setting of Pregnancy

- Potentially effective treatment for COVID-19 should not be withheld from pregnant women because of theoretical concerns related to the safety of therapeutic agents in pregnancy (AIII).
- Decisions regarding the use of drugs approved for other indications or investigational agents for the treatment of COVID-19 in pregnant patients must be made with shared decision-making between the patient and the clinical team, considering the safety of the medication for the woman and the fetus and the severity of maternal disease. For detailed guidance on the use of COVID-19 therapeutic agents in pregnancy, please refer to the pregnancy considerations subsection of each individual section of the Guidelines.
- To date, most SARS-CoV-2-related clinical trials have excluded, or included only a very few, pregnant women and lactating women. This limitation makes it difficult to make evidence-based recommendations on the use of SARS-CoV-2 therapies in these vulnerable patients and potentially limits their COVID-19 treatment options. When possible, pregnant women and lactating women should not be excluded from clinical trials of therapeutic agents or vaccines for SARS-CoV-2 infection.

Post-Delivery

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

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Special Considerations in Children

Last Updated: April 21, 2021

Summary Recommendations

- SARS-CoV-2 infection is generally milder in children than in adults, and a substantial proportion of children with the disease have asymptomatic infection.
- Most children with SARS-CoV-2 infection will not require any specific therapy.
- Children who have a history of medical complexity (e.g., due to neurologic impairment, developmental delays, or genetic syndromes including trisomy 21), obesity, chronic cardiopulmonary disease, or who are immunocompromised, as well as nonwhite children and older teenagers may be at increased risk for severe disease.
- There are limited data on the pathogenesis and clinical spectrum of COVID-19 disease in children. There are no pediatric data from placebo-controlled randomized clinical trials and limited data from observational studies to inform the development of pediatric-specific recommendations for the treatment of COVID-19.

Specific Therapy for Children

- In the absence of adequate data on the treatment of children with acute COVID-19, recommendations are based on outcome and safety data for adult patients and the child's risk of disease progression.
- Most children with mild or moderate disease can be managed with supportive care alone (**AIII**).
- **Remdesivir** is recommended for:
 - Hospitalized children aged ≥ 12 years with COVID-19 who have risk factors for severe disease and have an emergent or increasing need for supplemental oxygen (**BIII**).
 - Hospitalized children aged ≥ 16 years with COVID-19 who have an emergent or increasing need for supplemental oxygen regardless of whether they have risks factors for severe disease (**BIII**).
- In consultation with a pediatric infectious disease specialist, **remdesivir** can be considered for hospitalized children of all ages with COVID-19 who have an emergent or increasing need for supplemental oxygen (**CIII**).
- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using **dexamethasone** for hospitalized children with COVID-19 who require high-flow oxygen, noninvasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation (**BIII**).
- There are insufficient pediatric data for the Panel to recommend either for or against the use of anti-SARS-CoV-2 monoclonal antibody products for children with COVID-19 who are not hospitalized but who have risk factors for severe disease. Based on adult studies, bamlanivimab plus etesevimab or casirivimab plus imdevimab may be considered on a case-by-case basis for nonhospitalized children who meet Emergency Use Authorization (EUA) criteria for high-risk of severe disease, especially those who meet more than one criterion or are aged ≥ 16 years. The Panel recommends consulting a pediatric infectious disease specialist in such cases.
- The Panel **recommends against** the use of **convalescent plasma** for hospitalized children with COVID-19 who do not require mechanical ventilation, except in a clinical trial (**AIII**). The Panel **recommends against** the use of **convalescent plasma** for pediatric patients with COVID-19 who are mechanically ventilated (**AIII**). In consultation with a pediatric infectious disease specialist, high-titer convalescent plasma may be considered on a case-by-case basis for hospitalized children who meet the EUA criteria for its use.
- There are insufficient data 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 are insufficient data for the Panel to recommend either for or against the use of tocilizumab in hospitalized children with COVID-19 or multisystem inflammatory syndrome in children (MIS-C). The Panel **recommends against** the use of **sarilumab** for hospitalized children with COVID-19 or MIS-C, except in a clinical trial (**AIII**).
- MIS-C is a serious delayed complication of SARS-CoV-2 infection that may develop in a minority of children and young adults.
 - Consultation with a multidisciplinary team is recommended when considering and managing immunomodulating therapy for children with MIS-C (**AIII**). Intravenous immunoglobulin and/or corticosteroids are generally used as first-line therapy, although interleukin-1 antagonists have been used for refractory cases. The optimal choice and combination of immunomodulating therapies have not been definitively established.

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

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

Epidemiology

Data from the Centers for Disease Control and Prevention (CDC) demonstrate a lower incidence of SARS-CoV-2 infection and severe disease in children than in adults.¹ However, without more systematic testing for children, including for children with mild symptoms as part of contact tracing, or seroprevalence studies, the true burden of pediatric SARS-CoV-2 infection remains unclear. Data on the pathogenesis and disease severity of SARS-CoV-2 infection in children are increasing but are still limited compared to the data in adults. Several large epidemiologic studies suggest that severe manifestations of acute disease are substantially less common in children than in adults. Although only a small percentage of children with COVID-19 will require medical attention, intensive care unit (ICU)-admission rates for hospitalized children are comparable to those for hospitalized adults with COVID-19.²⁻¹⁰

Clinical Manifestations

The signs and symptoms of SARS-CoV-2 infection in children may be similar to those in adults, but most children may be asymptomatic or only have a few symptoms. The most common signs and symptoms of COVID-19 in hospitalized children are fever, nausea/vomiting, cough, shortness of breath, and upper respiratory symptoms.^{9,11} Of note, signs and symptoms of COVID-19 may overlap significantly with those of other viral infections, including influenza and other respiratory and enteric viral infections. Although the true incidence of asymptomatic SARS-CoV-2 infection is unknown, asymptomatic infection was reported in up to 45% of children who underwent surveillance testing at the time of hospitalization for a non-COVID-19 indication.¹²

SARS-CoV-2 has been associated with a potentially severe inflammatory syndrome in children and young adults (multisystem inflammatory syndrome in children [MIS-C]), which is discussed below.

Risk Factors

Data to clearly establish risk factors for severe COVID-19 in children are limited. Data reported to CDC show lower hospitalization rates and ICU admission rates for children with COVID-19 than for adults with the disease.^{11,13} COVID-19-related hospitalization rates for children were highest in children aged <2 years and higher in Hispanic and Black children than in White children. The majority of hospitalized children with acute COVID-19 had underlying conditions, with obesity, chronic lung disease, and prematurity (data collected only for children aged <2 years) being the most prevalent.¹⁴ Risk factors such as obesity may be more applicable to older teenagers.

In a large study of hospitalized children from the United Kingdom, age <1 month, age 10 to 14 years, and Black race were associated with admission to critical care unit on multivariate analysis.⁹ Another large multicenter study from Europe identified male sex, pre-existing medical conditions, and the presence of lower respiratory tract disease at presentation as additional risk factors for ICU admission in multivariable models.¹⁰

Deaths associated with COVID-19 among those aged <21 years are higher among children aged 10 to 20 years, especially young adults aged 18 to 20 years, as well as among Hispanic, Black, and American Indian/Alaska Native persons.¹⁵ A high proportion of the fatal cases of pediatric COVID-19 are in children with underlying medical conditions, most commonly chronic lung disease, obesity, and neurologic and developmental disorders.

Based on data for adults with COVID-19 and extrapolations from data for non-COVID-19 pediatric respiratory viral infections, severely immunocompromised children and those with underlying cardiopulmonary disease may be at higher risk for severe COVID-19. Initial reports of SARS-CoV-2 infection among pediatric patients with cancer and pediatric solid organ transplant recipients have demonstrated a low frequency of infection and associated morbidity;¹⁶⁻²⁰ however, similar reports for other immunocompromised pediatric populations are limited.²¹ A few reports have demonstrated a higher prevalence of asthma in pediatric COVID-19 cases, although the association of asthma with severe disease is not clearly defined.^{7,8} Congenital heart disease may be associated with increased risk of severe COVID-19, but the condition has not been consistently identified as a risk factor.^{22,23} Guidance on the treatment of COVID-19 in children endorsed by the Pediatric Infectious Diseases Society specifies additional risk factors to consider when making decisions about antiviral and monoclonal antibody therapy for pediatric patients.^{24,25}

Persistent symptoms after acute COVID-19 have been described in adults, although the incidence of this sequelae in children remains unknown and is an active area of research (see [Clinical Spectrum of SARS-CoV-2 Infection](#)). Cardiac imaging studies have described myocardial injury in young athletes who had only mild disease;²⁶ additional studies are needed to determine long-term cardiac sequelae.

Vertical Transmission and Infants Born to Mothers with SARS-CoV-2 Infection

Vertical transmission of SARS-CoV-2 is thought to be rare, but suspected or probable vertical transmission has been described.²⁷⁻²⁹ Initial data on perinatal transmission of SARS-CoV-2 were limited to small case series with conflicting results; some studies demonstrated lack of transmission, whereas others were not able to definitively rule out this possibility.³⁰⁻³³ Among 100 women with SARS-CoV-2 infection who delivered 101 infants, only two infants had equivocal reverse transcription polymerase chain reaction (RT-PCR) results that may have reflected SARS-CoV-2 infection even though most of the infants remained with their mothers, in rooms with infection prevention measures in place, and were breast fed.³⁴

Infants born to individuals with SARS-CoV-2 infection may have higher risk of poor clinical outcomes than those born to individuals without SARS-CoV-2 infection, although data are conflicting. In a systematic review of case series in pregnant women with confirmed SARS-CoV-2 infection (predominantly from China), the preterm birth rate was 20.1% (57 of 284 births were preterm; 95% CI, 15.8–25.1), the cesarean delivery rate was 84.7% (33 of 392 births were by cesarean delivery; 95% CI, 80.8–87.9), there was no vertical transmission, and the neonatal death rate was 0.3% (1 of 313 neonates died; 95% CI, 0.1–1.8).³⁵ In a prospective cohort study of 263 infants born in the United States, the rates for preterm births, neonatal ICU admissions, and respiratory disease did not differ between infants born to mothers with and without SARS-CoV-2 infection.³⁶ A cohort study from Sweden demonstrated that 5-minute Apgar scores and birth weight for gestational age did not differ between infants born to mothers with and without SARS-CoV-2 infection.³⁷ Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET) data from CDC that captured 598 hospitalized, pregnant women with SARS-CoV-2 infection showed a pregnancy loss rate of 2% among 458 pregnancies completed during COVID-19-related hospitalizations and a preterm birth rate of 12.9% compared to 10% for the general U.S. population.³⁸ A systematic review and meta-analysis of studies that included 2,567 pregnancies concluded that SARS-CoV-2-positive mothers were at increased risk of iatrogenic preterm birth. This risk was predominantly due to caesarean sections (21.8% of births) performed due to maternal illness and fear of maternal decompensation. In contrast, there was no increase in the rate of spontaneous preterm birth relative to the expected rate in pregnant individuals without SARS-CoV-2 infection.^{39,40} Finally, a prospective cohort study from the United Kingdom of 66 neonates with SARS-CoV-2 infection found that 3% may have had vertically acquired infection and 12% had suspected nosocomially acquired infection.²⁹ Specific guidance on the diagnosis

and management of COVID-19 in neonates born to mothers with known or suspected SARS-CoV-2 infection is provided by [CDC](#).

Treatment Considerations

There are no results available from clinical trials evaluating treatment for COVID-19 in children, and observational data on the safety or efficacy of drug therapy in children with COVID-19 are extremely limited. More high-quality studies, including randomized trials, are urgently needed. Guidance for the treatment of COVID-19 in children has been published and is mostly extrapolated from recommendations for adults with COVID-19.^{41,42} The older the child and the more severe the disease, the more reasonable it is to follow recommendations for adult patients with COVID-19 (see [Therapeutic Management of Adults With COVID-19](#)). To address the uncertain safety and efficacy of these treatment options, children should be enrolled in clinical trials and multicenter pragmatic trials whenever possible.

The majority of children with mild or moderate COVID-19 will not progress to more severe illness and thus should be managed with supportive care alone (**AIII**). The risks and benefits of therapy should be assessed based on illness severity, age, and the presence of risk factors outlined above.

Remdesivir

Remdesivir is the only drug approved by the Food and Drug Administration (FDA) for the treatment of COVID-19 (see [Remdesivir](#) for detailed information). It is approved for the treatment of COVID-19 in hospitalized adult and pediatric patients (aged ≥ 12 years and weighing ≥ 40 kg). It is also available through an FDA Emergency Use Authorization (EUA) for the treatment of COVID-19 in hospitalized pediatric patients weighing 3.5 kg to < 40 kg or aged < 12 years and weighing ≥ 3.5 kg.⁴³ Remdesivir has not been evaluated in clinical trials that include children, and there have been no results from systematic evaluations of pharmacokinetics, efficacy, or toxicity in younger children, although studies are ongoing (see [ClinicalTrials.gov](#)). However, based on adult data, the potential benefits of remdesivir are likely to be greater for hospitalized children with COVID-19 who are at higher risk of progression due to older age (i.e., aged ≥ 16 years) or medical condition than for those without these risk factors. **Remdesivir** is recommended for hospitalized children aged ≥ 12 years with COVID-19 who have risk factors for severe disease and have an emergent or increasing need for supplemental oxygen (**BIII**). **Remdesivir** is also recommended for hospitalized children aged ≥ 16 years with COVID-19 who have an emergent or increasing need for supplemental oxygen even in the absence of risk factors (**BIII**). **Remdesivir** can be considered for other hospitalized children of all ages with COVID-19 who have an emergent or increasing need for supplemental oxygen in consultation with a pediatric infectious disease specialist (**CIII**).

Dexamethasone

Dexamethasone is recommended for the treatment of hospitalized adults with COVID-19 who require mechanical ventilation or supplemental oxygen through a high-flow device (see [Corticosteroids](#) and [Therapeutic Management of Adults With COVID-19](#) for detailed information). The safety and effectiveness of dexamethasone or other corticosteroids for COVID-19 treatment have not been sufficiently evaluated in pediatric patients and thus caution is warranted when extrapolating recommendations for adults to patients aged < 18 years. The COVID-19 Treatment Guidelines Panel (the Panel) recommends using **dexamethasone** for children with COVID-19 who require high-flow oxygen, noninvasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) (**BIII**). It is not routinely recommended for pediatric patients who require only low levels of oxygen support (i.e., via a nasal cannula only). Use of dexamethasone for the treatment of severe COVID-19 in children who are profoundly immunocompromised has not been evaluated, may be harmful, and therefore should be considered only on a case-by-case basis. If dexamethasone is not available, alternative glucocorticoids such as prednisone, methylprednisolone, or hydrocortisone can be

considered. The dexamethasone dosing regimen for pediatric patients is dexamethasone 0.15 mg/kg/dose (maximum dose 6 mg) once daily for up to 10 days.

Anti-SARS-CoV-2 Monoclonal Antibodies

Although EUAs have been issued for bamlanivimab plus etesevimab and casirivimab plus imdevimab for the treatment of nonhospitalized, high-risk patients aged ≥ 12 years and weighing ≥ 40 kg with mild to moderate COVID-19, there are currently no data available to determine which high-risk pediatric patients defined in the EUAs will likely benefit from these therapies. Consequently, there are insufficient data for the Panel to recommend either for or against the use of these monoclonal antibodies in children with COVID-19 who are not hospitalized but are at high risk of severe disease and/or hospitalization. In consultation with a pediatric infectious disease specialist, bamlanivimab plus etesevimab or casirivimab plus imdevimab can be considered on a case-by-case basis for children who meet the EUA criteria, but should not be considered routine care. This recommendation is primarily based on the absence of data assessing efficacy or safety in children or adolescents, limited data with which to identify children at the highest risk of severe COVID-19, as well as the low overall risk of progression to serious disease in children, and the potential risk associated with infusion reactions.

Additional guidance is provided in a recent publication endorsed by the Pediatric Infectious Diseases Society.²⁵ There are currently no data to support the use of anti-SARS-CoV-2 monoclonal antibodies in hospitalized children for COVID-19. Emerging data regarding the prevalence and clinical significance of SARS-CoV-2 variants, and the efficacy of monoclonal antibodies against variants, may inform the choice of specific anti-SARS-CoV-2 monoclonal antibody therapy in the future.

Convalescent Plasma

FDA has also issued an EUA for the use of high-titer convalescent plasma for the treatment of hospitalized patients with COVID-19 (see [Convalescent Plasma](#) for detailed information).⁴⁴ The safety and efficacy of convalescent plasma have not been evaluated in pediatric patients with COVID-19. There are insufficient data for the Panel to recommend either for or against the use of convalescent plasma for the treatment of COVID-19 in either pediatric outpatients or in hospitalized children who do not require mechanical ventilation. The Panel **recommends against** the use of **convalescent plasma** for pediatric patients with COVID-19 who are mechanically ventilated (**AIII**). In consultation with a pediatric infectious disease specialist, convalescent plasma may be considered on a case-by-case basis for children who meet the EUA criteria for its use.

Baricitinib

FDA has also issued an EUA for the use of baricitinib in combination with remdesivir in hospitalized adults and children aged ≥ 2 years with COVID-19 who require supplemental oxygen, invasive mechanical ventilation, or ECMO.⁴⁵ The safety and efficacy of baricitinib have not been evaluated in pediatric patients with COVID-19, and pediatric data regarding its use for other conditions are extremely limited. Thus, there are insufficient data for the Panel to recommend either for or against the use of baricitinib in combination with remdesivir for the treatment of COVID-19 in hospitalized children in whom corticosteroids cannot be used (see [Kinase Inhibitors](#) for detailed information).

Tocilizumab

Data on tocilizumab use for the treatment of non-COVID-19 conditions in children are limited to very specific clinical scenarios (e.g., chimeric antigen receptor T cell-related cytokine release syndrome).⁴⁶ The use of tocilizumab for severe cases of acute COVID-19 has been described in pediatric case series.^{14,47} Data on tocilizumab efficacy from trials in adults with COVID-19 are conflicting, and

benefit has only been demonstrated in a subset of hospitalized patients (see [Interleukin-6 Inhibitors](#)). There are insufficient data 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 are insufficient data for the Panel to recommend either for or against the use of specific antivirals or immunomodulatory agents for the treatment of COVID-19 in pediatric patients. Considerations, such as underlying conditions, disease severity, and potential for drug toxicity or drug interactions, may inform decisions on the use of these agents in pediatric patients with COVID-19 on a case-by-case basis. Children should be enrolled in clinical trials evaluating COVID-19 therapies whenever possible. A number of additional drugs are being investigated for the treatment of COVID-19 in adults; refer to the [Antiviral Therapy](#) and [Immunomodulators](#) sections to review special considerations for use of these drugs in children and refer to [Table 2d](#) and [Table 4b](#) for recommendations on pediatric dosing regimens.

Multisystem Inflammatory Syndrome in Children

A small subset of children and young adults with SARS-CoV-2 infection develop MIS-C. This immune manifestation is also referred to as pediatric multisystem inflammatory syndrome—temporally associated with SARS-CoV-2 (PMIS-TS), although the case definitions for the syndromes differ slightly. This syndrome was first described in Europe, where previously healthy children with severe inflammation and Kawasaki disease-like features were identified to have current or recent infection with SARS-CoV-2. The clinical spectrum of MIS-C has been described in the United States and is similar to that described for PIMS-TS. MIS-C is consistent with a post-infectious inflammatory syndrome related to SARS-CoV-2.^{48,49} Most MIS-C patients have serologic evidence of previous SARS-CoV-2 infection, but only a minority are RT-PCR positive for SARS-CoV-2 at presentation.^{50,51} The peak incidence of MIS-C lags about 4 weeks behind the peak of acute pediatric COVID-19 hospitalizations. Emerging data suggests that adults may also develop a similar syndrome, multisystem inflammatory syndrome in adults (MIS-A), although it is not clear if this is a postinfectious complication similar to MIS-C.⁵⁰⁻⁵² Although risk factors for MIS-C have not been established, in an analysis of MIS-C cases in the United States, most of the children were nonwhite, and obesity was the most common comorbidity.⁵³ Unlike in children with acute COVID-19, the majority of children who present with MIS-C do not seem to have underlying comorbid conditions other than obesity.

Clinical Manifestations

The current CDC case definition for MIS-C includes:

- An individual aged <21 years presenting with fever,^a laboratory evidence of inflammation,^b and evidence of clinically severe illness requiring hospitalization with multisystem (i.e., more than two) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological); *and*
- No alternative plausible diagnoses; *and*
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, antigen test, or serology; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms.⁵⁴

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

^b Including, but not limited to one or more of the following: an elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase, interleukin (IL)-6, or neutrophils, or reduced lymphocytes or albumin levels

Distinguishing MIS-C from other febrile illnesses in the community setting remains challenging, but presence of persistent fever, multisystem manifestations, and laboratory abnormalities could help early recognition.⁵⁵ The clinical spectrum of hospitalized cases has included younger children with mucocutaneous manifestations that overlap those with Kawasaki disease, older children with more multiorgan involvement and shock, and patients with respiratory manifestations that overlap with acute COVID-19. Patients with MIS-C are often critically ill and up to 80% of children require ICU admission.⁵³ Most patients with MIS-C have markers of cardiac injury or dysfunction, including elevated levels of troponin and brain natriuretic protein.^{50,51} Echocardiographic findings in these cases include impaired left ventricular function, as well as coronary artery dilations, and rarely, coronary artery aneurysms. Reported mortality rate in the United States for hospitalized children with MIS-C is 1% to 2%. Longitudinal studies are currently ongoing to examine the long-term sequelae of MIS-C.

The pathogenesis of MIS-C is still being elucidated. Differences have been demonstrated between MIS-C and typical Kawasaki disease in terms of epidemiology, cytopenias, cytokine expression, and elevation of inflammatory markers. Immunologic profiling has also shown differences in cytokine expression (tumor necrosis factor alpha and IL-10) between MIS-C and acute COVID-19 in children.⁵⁶⁻⁵⁸

Management

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

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Special Considerations in Adults and Children With Cancer

Last Updated: April 21, 2020

Summary Recommendations
<ul style="list-style-type: none">Given the effectiveness of the SARS-CoV-2 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 SARS-CoV-2 vaccination for patients with active cancer or patients who are receiving treatment for cancer (AIII). See the text below for information on the appropriate timing for SARS-CoV-2 vaccination in these patients.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 Antiviral Drugs That Are Approved or Under Evaluation for the Treatment of COVID-19 and Immunomodulators Under Evaluation for the Treatment of 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 The risk for immunosuppression and susceptibility to SARS-CoV-2 infection varies between cancer types, treatments administered, and stages of therapy (e.g., patients who are actively being treated compared to those in remission). In a study that used data from the COVID-19 and Cancer Consortium Registry, cancer patients who were in remission or who had no evidence of disease were at a lower risk of death from COVID-19 than those who were receiving active treatment.⁶ It is unclear whether cancer survivors are at increased risk for severe COVID-19 and its complications compared to people without a history of cancer.

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

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

This section of the COVID-19 Treatment Guidelines complements these sources and focuses on

considerations regarding testing for SARS-CoV-2, 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 SARS-CoV-2 in Patients With Cancer

The clinical trials that evaluated the SARS-CoV-2 vaccines that have received Emergency Use Authorizations from the Food and Drug Administration excluded severely immunocompromised patients. The Advisory Committee on Immunization Practices notes that the authorized SARS-CoV-2 vaccines are not live vaccines; therefore, they can be safely administered to immunocompromised people.⁷ Given the effectiveness of the SARS-CoV-2 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 SARS-CoV-2 vaccination for patients with active cancer or patients who are receiving treatment for cancer (**AIII**).

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.⁸⁻¹⁰

When determining the timing of SARS-CoV-2 vaccination in patients with cancer, clinicians should consider the following factors:

- If possible, patients who are planning to receive chemotherapy should complete vaccination for SARS-CoV-2 at least 2 weeks before starting chemotherapy.^{11,12}
- 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.¹³
- Hematopoietic stem cell and chimeric antigen receptor T cell recipients can be offered SARS-CoV-2 vaccination starting at least 3 months after therapy.¹²

It is unknown whether the immune response to SARS-CoV-2 vaccination can increase the risk of graft-versus-host disease or other immune-related complications. Studies of responses to influenza vaccination have shown that the immune response in cancer patients varies based on the type of cancer, whether the patient has received chemotherapy recently, and the type of chemotherapy.^{14,15} Additional research is needed to understand the vaccine response in patients with cancer. Outside of a clinical study, antibody testing **is not recommended** to assess immunity to SARS-CoV-2 following vaccination in patients with cancer. For people who received COVID-19 vaccines during chemotherapy or treatment with other immunosuppressive drugs, revaccination after they regain immune competence is currently **not recommended**.⁷

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.

Testing for COVID-19 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 risk

of developing neutropenia. A retrospective study suggests that cancer patients with neutropenia have a higher mortality rate if they develop COVID-19.¹⁶ Due to the potential risk of poor clinical outcomes in the setting of neutropenia and/or during the perioperative period, the Panel recommends performing molecular diagnostic testing for SARS-CoV-2 prior to procedures that require anesthesia and before initiating cytotoxic chemotherapy and long-acting biologic therapy **(BIII)**.^{17,18}

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. The Centers for Disease Control and Prevention published a framework to help clinicians decide whether a patient should receive in-person or virtual care during the COVID-19 pandemic; this framework accounts for factors such as the potential harm of delayed care and the degree of SARS-CoV-2 transmission in a patient's community.¹⁹ Telemedicine may improve access to providers for medically or socially vulnerable populations but could worsen disparities if these populations have limited access to technology. Nosocomial transmission of SARS-CoV-2 to patients and health care workers has been reported.²⁰⁻²² Principles of physical distancing and prevention strategies, including masking patients and health care workers and practicing hand hygiene, apply to all in-person interactions.²³

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

- If possible, treatment delays should be avoided for curable cancers that have been shown to have worse outcomes when treatment is delayed (e.g., pediatric acute lymphoblastic leukemia).
- When deciding between equally effective treatment regimens, regimens that can be administered orally or those that require fewer infusions are preferred.^{24,25}
- 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.²⁶
- Preventing neutropenia can decrease the risk of neutropenic fever and the need for emergency department evaluation and hospitalization during the COVID-19 pandemic. Granulocyte colony-stimulating factor (G-CSF) should be given with chemotherapy regimens that have intermediate (10% to 20%) or high (>20%) risk of febrile neutropenia.²⁷
- Cancer treatment regimens that do not affect outcomes of COVID-19 in cancer patients may not need to be altered. In a prospective observational study, receipt of immunotherapy, hormonal therapy, or radiotherapy in the month prior to SARS-CoV-2 infection was not associated with an increased risk of mortality among cancer patients with COVID-19.²⁸ 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).²⁹ A small cohort study of patients with prostate cancer from Finland did not find an association between androgen deprivation and incidence of SARS-CoV-2 infection.³⁰ The viral spike proteins that SARS-CoV-2 uses to enter cells are primed by TMPRSS2, an androgen-regulated gene. Whether androgen deprivation therapy protects against SARS-CoV-2 infection requires further investigation in larger cohorts or clinical trials.²⁹

- Radiation therapy guidelines suggest increasing the dose per fraction and reducing the number of daily treatments in order to minimize the number of hospital visits during the COVID-19 pandemic.^{24,25}

Blood supply shortages will likely continue during the COVID-19 pandemic due to social distancing, cancellation of blood drives, and infection among donors. Revised donor criteria have been proposed by the Food and Drug Administration to increase the number of eligible donors.³¹ In patients with cancer, lowering the transfusion thresholds for blood products (e.g., red blood cells, platelets) in asymptomatic patients should be considered.^{32,33} At this time, there is no evidence that COVID-19 can be transmitted through blood products.^{34,35}

Febrile Neutropenia

Cancer patients with febrile neutropenia should undergo molecular diagnostic testing for SARS-CoV-2 and evaluation for other infectious agents; they should also be given empiric antibiotics, as outlined in the NCCN Guidelines.³⁶ 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.³⁶ 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.^{37,38}

Recommendations for the treatment of COVID-19 are the same for cancer patients as for the general population (**AIII**). See [Antiviral Drugs That Are Approved or Under Evaluation for the Treatment of COVID-19](#) and [Immunomodulators Under Evaluation for the Treatment of COVID-19](#) for more information. Dexamethasone treatment has been associated with a lower mortality rate in patients with COVID-19 who require supplemental oxygen or invasive mechanical ventilation.³⁹ In cancer patients, dexamethasone is commonly used to prevent chemotherapy-induced nausea, as a part of tumor-directed therapy, and to treat inflammation associated with brain metastasis. The side effects of 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 discontinuing G-CSF and granulocyte-macrophage colony-stimulating factor in patients with cancer and acute SARS-CoV-2 infection who do not have bacterial or fungal infections to avoid the hypothetical risk of increasing inflammatory cytokine levels and pulmonary inflammation.^{27,40} Secondary infections (e.g., invasive pulmonary aspergillosis) have been reported in critically ill patients with COVID-19.^{41,42}

Decisions about administering cancer-directed therapy to patients with acute COVID-19 and those who are recovering from COVID-19 should be made on a case-by-case basis; clinicians should consider the indication for chemotherapy, the goals of care, and the patient's history of tolerance to the treatment (**BIII**). The optimal duration of time between resolution of infection and initiating or restarting cancer-directed therapy is unclear. Withholding treatment until COVID-19 symptoms have resolved is recommended, if possible. Prolonged viral shedding (detection of SARS-CoV-2 by molecular testing) may occur in cancer patients,² although it is unknown how this relates to infectious virus and how it

impacts outcomes. Therefore, there is no role for repeat testing in those recovering from COVID-19, and the decision to restart cancer treatments in this setting should be made on a case-by-case basis. The Panel recommends that clinicians who are treating COVID-19 in patients with cancer consult 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 cancer patients. Clinicians should pay careful attention to potential drug-drug interactions and overlapping toxicities between drugs that are used to treat COVID-19 and cancer-directed therapies, prophylactic antimicrobials, corticosteroids, and other medications (AIII).

Several antineoplastic medications have known interactions with therapies that are being investigated for COVID-19.³² 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 cancer patients and is recommended for the treatment of certain patients with COVID-19 (see [Therapeutic Management of 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. Lopinavir/ritonavir is a CYP3A4 inhibitor, and it can increase methotrexate, vincristine, or ruxolitinib concentrations. Lopinavir/ritonavir **is not recommended** for the treatment of COVID-19; however, patients may receive it in a clinical trial. In general, concomitant use of lopinavir/ritonavir and CYP3A4 substrates should be avoided. If lopinavir/ritonavir is used in combination with a cytotoxic drug that is also a CYP3A4 substrate, clinicians should monitor for toxicities of the cytotoxic drug and adjust the dose if necessary.

Special Considerations in Children

Preliminary published reports suggest that pediatric patients with cancer may have milder manifestations of COVID-19 than adult patients with cancer, although larger studies are needed.⁴³⁻⁴⁵ Guidance on managing children with cancer during the COVID-19 pandemic is available from an international group with input from the International Society of Paediatric Oncology, the Children's Oncology Group, St. Jude Global, and Childhood Cancer International.⁴⁶ 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.^{46,47} Special considerations for using antivirals in immunocompromised children, including those with malignancy, are available in a multicenter guidance statement.⁴⁸

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

Last Updated: April 21, 2021

Summary Recommendations

Vaccination for SARS-CoV-2

- Given the effectiveness of SARS-CoV-2 vaccines in the general population and the increased risk of worse clinical outcomes of COVID-19 in transplant and cellular therapy recipients, the COVID-19 Treatment Guidelines Panel (the Panel) recommends SARS-CoV-2 vaccination for potential transplant and cellular therapy candidates, potential donors, and recipients **(AIII)**. See the text below for information on the appropriate timing for SARS-CoV-2 vaccination in these patients.

Potential Transplant and Cellular Therapy Candidates

- The Panel recommends diagnostic molecular testing for SARS-CoV-2 for all potential solid organ transplant (SOT), hematopoietic cell transplant (HCT), and cell therapy candidates with signs and symptoms that suggest acute COVID-19 infection **(AIII)**.
- The Panel recommends following the guidance from medical professional organizations that specialize in providing care for SOT, HCT, or cell therapy recipients when performing diagnostic molecular testing for SARS-CoV-2 in these patients **(AIII)**.
- If SARS-CoV-2 is detected or if infection is strongly suspected, transplantation should be deferred, if possible **(BIII)**.

Potential Transplant Donors

- The Panel recommends assessing all potential SOT 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 Therapy Recipients With COVID-19

- Clinicians should follow the guidelines for evaluating and managing COVID-19 in nontransplant patients when treating transplant and cellular therapy recipients **(AIII)**. See [Therapeutic Management of Adults With COVID-19](#) for more information.
- The Panel recommends that clinicians who are treating COVID-19 in transplant and cellular therapy patients consult with a transplant specialist before adjusting immunosuppressive medications **(AIII)**.
- When treating COVID-19, clinicians should pay careful attention to potential drug-drug interactions and overlapping toxicities with immunosuppressants, prophylactic antimicrobials, and other medications **(AIII)**.

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

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

Introduction

Treating COVID-19 in solid organ transplant (SOT), hematopoietic cell transplant (HCT), and cellular immunotherapy recipients can be challenging due to the presence of coexisting medical conditions, transplant-related cytopenias, and the need for chronic immunosuppressive therapy to prevent graft rejection and graft-versus-host disease. Transplant recipients may also potentially have increased exposure to SARS-CoV-2 given their frequent contact with the health care system. Since immunosuppressive agents modulate several aspects of the host's immune response, the severity of COVID-19 could potentially be affected by the type and the intensity of the immunosuppressive

effect of the agent, as well as by specific combinations of immunosuppressive agents. Some transplant recipients have medical comorbidities that have been associated with more severe cases of COVID-19 and a greater risk of mortality, which makes the attributable impact of transplantation on disease severity difficult to assess.

The American Association for the Study of Liver Diseases (AASLD),¹ the [International Society for Heart and Lung Transplantation](#), the [American Society of Transplantation](#), the [American Society for Transplantation and Cellular Therapy \(ASTCT\)](#), the [European Society for Blood and Marrow Transplantation \(EBMT\)](#), and the [Association of Organ Procurement Organizations](#) provide guidance for clinicians who are caring for transplant recipients with COVID-19, as well as guidance for screening potential donors and transplant or cell therapy candidates. This section of the COVID-19 Treatment Guidelines complements these sources and focuses on considerations for managing COVID-19 in SOT, HCT, and cellular therapy recipients. The optimal management and therapeutic approach to COVID-19 in these populations is unknown. At this time, the procedures for evaluating and managing COVID-19 in transplant recipients are the same as those for nontransplant patients (AIII). See [Therapeutic Management of 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 SARS-CoV-2 in Solid Organ Transplant, Hematopoietic Stem Cell Transplant, and Cellular Therapy Candidates, Donors, and Recipients

The clinical trials that have evaluated the SARS-CoV-2 vaccines that have received Emergency Use Authorizations from the Food and Drug Administration have excluded severely immunocompromised patients.²⁻⁴ The Advisory Committee on Immunization Practices notes that the currently authorized COVID-19 vaccines are not live vaccines; therefore, they can be safely administered to immunocompromised people.⁵ The efficacy rates for the available vaccines may be lower in immunocompromised patients than in the general population, and the relative efficacy of the different vaccines for transplant candidates or recipients is currently unknown. Given the effectiveness of SARS-CoV-2 vaccines in the general population and the increased risk of worse clinical outcomes of COVID-19 in transplant and cellular therapy recipients, the COVID-19 Treatment Guidelines Panel (the Panel) recommends SARS-CoV-2 vaccination for potential transplant and cellular therapy candidates, potential donors, and recipients (AIII).

When determining the timing of SARS-CoV-2 vaccination in SOT, HCT, and cell therapy recipients, clinicians should consider the following factors:

- Ideally, SOT candidates should receive SARS-CoV-2 vaccines while they are awaiting transplant.
- In general, vaccination should be completed at least 2 weeks prior to SOT or started 1 month after SOT.
- In certain situations, it may be appropriate to delay vaccination until 3 months after SOT, such as when T cell or B cell ablative therapy (with antithymocyte globulin or rituximab) is used at the time of transplant.⁶
- At this time, reducing the dose of immunosuppressants and holding immunosuppressants prior to SARS-CoV-2 vaccination **are not recommended**.
- SARS-CoV-2 vaccines can be offered as early as 3 months after a patient receives HCT or chimeric antigen receptor T cell (CAR-T) therapy, although the efficacy of the vaccines may be reduced compared to the efficacy observed in the general population.^{7,8} Patients who are scheduled to receive cytotoxic or B cell–depleting therapies should complete their SARS-CoV-2 vaccination prior to initiation or between cycles of cytotoxic or B cell–depleting therapies if possible.

- After completing SARS-CoV-2 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).⁹

It is unknown whether the immune responses to SARS-CoV-2 vaccination can increase the risk of graft-versus-host disease or other immune-related complications. Outside of a clinical study, antibody testing **is not recommended** to assess immunity to SARS-CoV-2 following COVID-19 vaccination in transplant patients. For people who received COVID-19 vaccines during treatment with immunosuppressive drugs, revaccination after they regain immune competence is currently not recommended.

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.

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

The risk of transmission of SARS-CoV-2 from donors to candidates is unknown. The probability 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. 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.¹⁰ HCT donors should practice good hygiene and avoid crowded places and large group gatherings during the 28 days prior to donation.¹¹

Assessment of Transplant and Cellular Therapy Candidates

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

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

Assessment of Donors

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

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

If SARS-CoV-2 is detected or if infection is strongly suspected in a potential SOT donor or candidate, transplant should be deferred, if possible (**BIII**). The optimal disease-free interval before transplantation is not known. The risks of viral transmission should be balanced against the risks to the candidate,

such as progression of the underlying disease and risk of mortality if the candidate does not receive the transplant. This decision should be continually reassessed as conditions evolve. For HCT and cellular therapy candidates, current guidelines recommend deferring transplants or immunotherapy procedures, including peripheral blood stem cell mobilization, bone marrow harvest, T cell collection, and conditioning/lymphodepletion in recipients who test positive for SARS-CoV-2 or who have clinical symptoms that are consistent with infection. Final decisions should be made on a case-by-case basis while weighing the risks of delaying or altering therapy for the underlying disease.

Transplant Recipients With COVID-19

SOT recipients who are receiving immunosuppressive therapy should be considered to be at increased risk for severe COVID-19.^{1,12} A national survey of 88 U.S. transplant centers conducted between March 24 and 31, 2020, reported that 148 SOT recipients received a diagnosis of COVID-19 infection (69.6% were kidney recipients, 15.5% were liver recipients, 8.8% were heart recipients, and 6.1% were lung recipients).¹³ COVID-19 was mild in 54% of recipients and moderate in 21% of recipients, and 25% of recipients were critically ill. Modification of immunosuppressive therapy during COVID-19 and the use of investigational therapies for treatment of COVID-19 varied widely among recipients. Initial reports of transplant recipients who were hospitalized with COVID-19 suggest mortality rates of up to 28%.¹⁴⁻¹⁸

Risk of Graft Rejection

There have been no published reports of graft rejection in SOT recipients who received a diagnosis of COVID-19, although this may be due to a limited ability to perform biopsies. Acute cellular rejection should not be presumed in SOT recipients without biopsy confirmation, 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.¹

There are limited data on the incidence and clinical characteristics of SARS-CoV-2 infection in [HCT](#) and [cellular therapy 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.¹⁹ 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 therapy 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.²⁰ Additional factors that have been used to determine the clinical severity of other respiratory viral infections include the degree of cytopenia, the intensity of the conditioning regimen, the graft source, the degree of mismatch, and the need for further immunosuppression to manage graft-versus-host disease. Prolonged viral shedding has been described in SOT and HCT recipients; this can have implications for infection prevention and for the timing of potential therapeutic interventions.²¹

Treatment of COVID-19 in Transplant Recipients

Currently, the antiviral agent remdesivir is the only drug that is approved by the Food and Drug Administration (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 monoclonal antibodies that are available through Emergency Use Authorizations (see [Anti-SARS-CoV-2 Monoclonal Antibodies](#)). Transplant recipients who are hospitalized with mild to

moderate COVID-19 may be considered for anti-SARS-CoV-2 monoclonal antibodies 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.²² Tocilizumab 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](#)).^{23,24} The risks and benefits of using both dexamethasone and tocilizumab in transplant recipients with COVID-19 who are receiving immunosuppressive therapy are unknown. Because both dexamethasone and tocilizumab are immunosuppressive agents, patients who receive this combination should be closely monitored for secondary infections.

The Panel's recommendations for the use of remdesivir, dexamethasone, and tocilizumab in patients with COVID-19 can be found in [Therapeutic Management of 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 are the same for transplant recipients as for the general population. When possible, treatment should be given as part of a clinical trial. The safety and efficacy of investigational agents and drugs that have been approved by the FDA for other indications are not well-defined in transplant recipients. Moreover, it is unknown whether concomitant use of immunosuppressive agents to prevent allograft rejection in the setting of COVID-19 affects treatment outcome.

Clinicians should pay special attention to the potential for drug-drug interactions and overlapping toxicities with concomitant medications, such as immunosuppressants that are used to prevent allograft rejection (e.g., corticosteroids, mycophenolate, and calcineurin inhibitors such as tacrolimus and cyclosporine), antimicrobials that are used to prevent opportunistic infections, and other medications. Dose modifications may be necessary for drugs that are used to treat COVID-19 in transplant recipients with pre-existing organ dysfunction. Adjustments to the immunosuppressive regimen should be individualized based on disease severity, the specific immunosuppressants used, the type of transplant, the time since transplantation, the drug concentration, and the risk of graft rejection.¹⁵ 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) are associated with elevated levels of transaminases. For liver transplant recipients, the AASLD does not consider abnormal liver biochemistries a contraindication to using remdesivir.²⁵ 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.²⁶ 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 [2d](#), [3c](#), and [4c](#).

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Special Considerations in People With HIV

Last Updated: April 21, 2021

Summary Recommendations

Prevention of COVID-19

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends that people with HIV receive SARS-CoV-2 vaccines regardless of their CD4 T lymphocyte cell count or HIV viral load, because the potential benefits outweigh the potential risks **(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 the same as those for the general population **(AIII)**.
- In people with advanced HIV and suspected or documented COVID-19, HIV-associated opportunistic infections (OIs) should also be considered in the differential diagnosis of febrile illness **(AIII)**.
- When starting treatment for COVID-19 in 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 of vaccines and potential treatments for SARS-CoV-2 infection.

Management of HIV

- People with HIV who develop COVID-19, including those who require hospitalization, should continue their antiretroviral therapy (ART) and OI prophylaxis whenever possible **(AIII)**.
- Clinicians 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)**.
- For people who present with COVID-19 and a new diagnosis of HIV, clinicians should consult an HIV specialist to determine the optimal time to initiate ART.

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

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

Introduction

Approximately 1.2 million persons in the United States are living with HIV. Most of these individuals are in care, and many are on antiretroviral therapy (ART) and have well-controlled disease.¹ Similar to COVID-19, HIV disproportionately affects racial and ethnic minorities and persons of lower socioeconomic status in the United States;² these demographic groups also appear to have a higher risk for severe outcomes with COVID-19. Information on SARS-CoV-2/HIV coinfection is evolving rapidly. The sections below outline the current state of knowledge regarding the prevention and diagnosis of SARS-CoV-2 infection in people with HIV, treatment and clinical outcomes in people with HIV who develop COVID-19, and management of HIV during the COVID-19 pandemic. In addition to these Guidelines, the Department of Health and Human Services (HHS) Panel on Antiretroviral Guidelines for Adults and Adolescents has developed the [Interim Guidance for COVID-19 and Persons with HIV](#).

Clinical Outcomes of COVID-19 in People With HIV

Data are emerging on the clinical outcomes of COVID-19 in people with HIV. In a case series of people with COVID-19 in Europe and the United States, no significant differences were observed in the clinical outcomes for COVID-19 between people with HIV and people who did not have HIV.³⁻¹⁰ For example, the Veterans Aging Cohort Study compared the clinical outcomes for 253 veterans with HIV and COVID-19 and the outcomes for a matched comparator arm of 504 veterans without HIV who developed COVID-19. More than 95% of the participants in this study were male. In this comparison, no differences were found between the outcomes for patients with HIV and those who did not have HIV.¹¹

In contrast, worse outcomes for patients with HIV and COVID-19, including increased COVID-19 mortality rates, have been reported by subsequent cohort studies in the United States, the United Kingdom, and South Africa.¹²⁻¹⁷ 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/mm³) 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 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 acquisition of 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 the acquisition of SARS-CoV-2 infection.

People with HIV should receive SARS-CoV-2 vaccines, regardless of their CD4 count or HIV viral load, because the potential benefits outweigh the potential risks (**AIII**). People with HIV were included in the clinical trials of the two mRNA vaccines and the adenovirus vector vaccine that are currently available through Emergency Use Authorizations (EUAs) from the Food and Drug Administration,¹⁸⁻²⁰ however, the safety and efficacy of these vaccines in people with HIV have not been reported. Typically, people with HIV who are on antiretroviral therapy (ART) and who have achieved virologic suppression respond well to licensed vaccines. Guidance for using these vaccines, including guidance for people with HIV, is available through the Advisory Committee on Immunization Practices (ACIP). A patient's HIV status should be kept confidential when administering a vaccine.

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 (see [Testing for SARS-CoV-2 Infection](#)) (**AIII**). There is currently no evidence that the performance characteristics of nucleic acid amplification testing 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.²¹

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/mm³. Persons with HIV who have a CD4 count of ≥ 500 cells/mm³ have similar cellular immune function to persons

without HIV. In people with HIV, a CD4 count <200 cells/mm³ 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 persons with advanced HIV who have presented with COVID-19 and another coinfection, including *Pneumocystis jirovecii* pneumonia.^{22,23} 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 persons with HIV in the United States are aged >50 years, and many have comorbidities that are associated with more severe illness with COVID-19, including hypertension, diabetes mellitus, cardiovascular disease, tobacco use disorder, chronic lung disease, chronic liver disease, and cancer.²⁴

There are a number of case reports and case series that describe the clinical presentation of COVID-19 in persons with HIV.^{3-10,25,26} These studies indicate that the clinical presentation of COVID-19 is similar in persons with and without HIV. Most of the published reports describe populations in which most of the individuals with HIV are on ART and have achieved virologic suppression. Consequently, the current understanding of the impact of COVID-19 in persons 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 that for persons without HIV (**AIII**). In outpatients, people with HIV who are immunosuppressed or who have certain underlying comorbidities are candidates for the monoclonal antibodies that are available through EUAs.²⁷⁻²⁹ In hospitalized patients, the appropriate treatment strategy depends on disease severity (see [Therapeutic Management of Adults With COVID-19](#)).

When starting treatment for COVID-19 in patients with HIV, clinicians should pay careful attention to potential drug-drug interactions and overlapping toxicities among COVID-19 treatments, ARV medications, antimicrobial therapies, and other medications (**AIII**). Both tocilizumab and dexamethasone, which are recommended for some patients with severe or critical COVID-19, are immunosuppressive agents. The safety of using these drugs in immunocompromised patients, including those with advanced HIV, has not been studied. Therefore, patients with advanced HIV who are receiving these drugs should be closely monitored for secondary infections. Dexamethasone is a dose-dependent inducer of cytochrome P450 3A4 and 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. Whether administering up to 10 days of dexamethasone impacts the clinical efficacy of other ARV drugs is unknown. Patients with HIV who are receiving dexamethasone for COVID-19 should follow up with their HIV providers to assess virologic response.

Although some ARV drugs are being studied for the prevention and treatment of COVID-19, no agents have been shown to be effective.

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

Management of HIV in People With SARS-CoV-2/HIV Coinfection

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

- 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**). ARV 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 for off-label use for the treatment or prevention of SARS-CoV-2 infection. To date, lopinavir/ritonavir and darunavir/ritonavir have not been found to be effective (see [Lopinavir/Ritonavir and Other HIV Protease Inhibitors](#)).^{30,31} 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.^{12,26}
- 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 for a patient with a feeding tube to continue an effective ARV regimen. Information may be available in the drug product label or in [this document](#).
- For people who present with COVID-19 and have either a new diagnosis of HIV or a history of HIV but are not taking ART, the optimal time to start or restart ART is currently unknown. For people with HIV who have not initiated ART or who have been off therapy for >2 weeks before presenting with COVID-19, the Panel recommends consulting an HIV specialist regarding initiation or re-initiation of ART as soon as clinically feasible. If ART is started, maintaining treatment and linking patients to HIV care upon hospital discharge is critical. If an HIV specialist is not available, clinical consultation is available by phone through the [National Clinical Consultation Center](#), Monday through Friday, 9 am to 8 pm EST.

Special Considerations in Children and Pregnant Women With HIV Who Develop COVID-19

Currently, there is limited information about pregnancy and maternal outcomes in women with HIV who have COVID-19 and in children with HIV and COVID-19. Please see the sections in these Guidelines

that discuss the management of COVID-19 during [pregnancy](#) and in [children](#), and the [HHS Interim Guidance for COVID-19 and Persons With HIV](#).

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Influenza and COVID-19

Last Updated: October 22, 2020

Summary Recommendations

Influenza Vaccination

- Although data are lacking on influenza vaccination for persons with COVID-19, on the basis of practice for other acute respiratory infections, the Panel recommends that persons with COVID-19 should receive an inactivated influenza vaccine (**BIII**). The Centers for Disease Control and Prevention (CDC) has provided guidance on the timing of influenza vaccination for inpatients and outpatients with COVID-19 (see [Interim Guidance for Routine and Influenza Immunization Services During the COVID-19 Pandemic](#)).

Diagnosis of Influenza and COVID-19 When Influenza Viruses and SARS-CoV-2 Are Cocirculating

- Only testing can distinguish between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and influenza virus infections and identify SARS-CoV-2 and influenza virus coinfection.
- When SARS-CoV-2 and influenza viruses are cocirculating, the Panel recommends testing for both viruses in all hospitalized patients with acute respiratory illness (**AIII**).
- When SARS-CoV-2 and influenza viruses are cocirculating, the Panel recommends influenza testing in outpatients with acute respiratory illness if the results will change clinical management of the patient (**BIII**).
- Testing for other pathogens should be considered depending on clinical circumstances, especially in patients with influenza in whom bacterial superinfection is a well-recognized complication.
- See the CDC [Information for Clinicians on Influenza Virus Testing](#) and the [Infectious Diseases Society of America \(IDSA\) Clinical Practice Guidelines](#) for more information.

Antiviral Treatment of Influenza When Influenza Viruses and SARS-CoV-2 Are Cocirculating

- The treatment of influenza is the same in all patients regardless of SARS-CoV-2 coinfection (**AIII**).
- The Panel recommends that hospitalized patients be started on empiric treatment for influenza with oseltamivir as soon as possible without waiting for influenza testing results (**AIIb**).
 - Antiviral treatment of influenza can be stopped when influenza has been ruled out by nucleic acid detection assay in upper respiratory tract specimens for nonintubated patients and in both upper and lower respiratory tract specimens for intubated patients.
- For influenza treatment in hospitalized and non-hospitalized patients, see the [CDC](#) and [IDSA](#) recommendations on antiviral treatment of influenza.

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

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

Introduction

Influenza activity in the United States during the 2020–2021 influenza season is difficult to predict and could vary geographically and by the extent of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) community mitigation measures. During early 2020, sharp declines in influenza activity coincided with implementation of SARS-CoV-2 control measures in the United States and several Asian countries.¹⁻⁴ Very low influenza virus circulation was observed in Australia, Chile, and South Africa during the typical Southern Hemisphere influenza season in 2020.⁵ Clinicians should monitor local influenza and SARS-CoV-2 activity (e.g., by tracking local and state public health surveillance data and testing performed at health care facilities) to inform evaluation and management of patients with acute respiratory illness.

Influenza Vaccination

There are no data on the safety, immunogenicity, or effectiveness of influenza vaccines in patients

with mild COVID-19 or those who are recovering from COVID-19. Therefore, the optimal timing for influenza vaccination in these patients is unknown. The safety and efficacy of vaccinating persons who have mild illnesses from other etiologies have been documented.⁶ On the basis of practice following other acute respiratory infections, the Panel recommends that persons with COVID-19 should receive an inactivated influenza vaccine (**BIII**). The Centers for Disease Control and Prevention (CDC) has provided guidance on the timing of influenza vaccination for inpatients and outpatients with COVID-19 (see [Interim Guidance for Routine and Influenza Immunization Services During the COVID-19 Pandemic](#)). It is not known whether dexamethasone or other immunomodulatory therapies for COVID-19 will affect the immune response to influenza vaccine. However, despite this uncertainty, as long as influenza viruses are circulating, an unvaccinated person with COVID-19 should receive the influenza vaccine once they have substantially improved or recovered from COVID-19. See influenza vaccine recommendations from [CDC](#) and the [Advisory Committee on Immunization Practices](#).

Clinical Presentation of Influenza Versus COVID-19

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

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

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

Which Patients Should Receive Antiviral Treatment of Influenza?

When SARS-CoV-2 and influenza viruses are cocirculating in the community, patients who require hospitalization and are suspected of having either or both viral infections should receive influenza antiviral treatment with oseltamivir as soon as possible without waiting for influenza testing results (**AIIb**).¹⁴ Treatment for influenza is the same for all patients regardless of SARS-CoV-2 coinfection (**AIII**). See the [CDC Influenza Antiviral Medications: Summary for Clinicians](#), including [clinical algorithms](#) for antiviral treatment of patients with suspected or confirmed influenza when SARS-CoV-2

and influenza viruses are cocirculating, and the [IDSA Clinical Practice Guidelines](#) recommendations on antiviral treatment of influenza.

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

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

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

- Corticosteroids, which may be used for the treatment of COVID-19, may prolong influenza viral replication and viral RNA detection and may be associated with poor outcomes.^{14,15}
- Oseltamivir has no activity against SARS-CoV-2.¹⁶ Oseltamivir does not have any known interactions with remdesivir.
- Standard-dose oseltamivir is well absorbed even in critically ill patients. For patients who cannot tolerate oral or enterically administered oseltamivir (e.g., because of gastric stasis, malabsorption, or gastrointestinal bleeding), intravenous peramivir is an option.¹⁴ There are no data on peramivir activity against SARS-CoV-2.
- CDC does not recommend inhaled zanamivir and oral baloxavir for the treatment of influenza in hospitalized patients because of insufficient safety and efficacy data (see the [CDC Influenza Antiviral Medications: Summary for Clinicians](#)). There are no data on zanamivir activity against SARS-CoV-2. Baloxavir has no activity against SARS-CoV-2.¹⁶
- Based upon limited data, the co-occurrence of community-acquired secondary bacterial pneumonia with COVID-19 appears to be infrequent and may be more common with influenza.^{17,18} Typical bacterial causes of community-acquired pneumonia with severe influenza are *Staphylococcus aureus* (methicillin-resistant *S. aureus* [MRSA] and methicillin-susceptible *S. aureus* [MSSA]), *Streptococcus pneumoniae*, and group A *Streptococcus*.¹⁴
- Patients with COVID-19 who develop new respiratory symptoms with or without fever or respiratory distress, and without a clear diagnosis, should be evaluated for the possibility of nosocomial influenza.

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

Last Updated: April 21, 2021

Name	Affiliation
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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: Month Day, 2021

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

Panel Member	Financial Disclosure	
	Company	Relationship
Judith Aberg, MD	Atea Pharmaceuticals	Research Support
	Emergent BioSolutions	Research Support
	Gilead Sciences	Research Support
	Pfizer	Research Support
	Regeneron	Research Support
Adaora Adimora, MD, MPH	Gilead Sciences	Research Support
	Merck & Co.	Advisory Board, Consultant
Jason Baker, MD, MS	Gilead Sciences	Research Support
	Humanigen, Inc.	Research Support
Lisa Baumann Kreuziger, MD, MS	3M	Stockholder, Spouse Is Employee
	Quercis Pharma AG	Advisory Board for Nonapproved Medications
	Versiti	Employee
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	Merck & Co.	Advisory Board
	ViiV Healthcare	Advisory Board, Research Support
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	Gilead Sciences	Consultant, Research Support
	Merck & Co.	Consultant, Research Support
	ViiV Healthcare	Research Support
Richard T. Davey, Jr., MD	None	N/A
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Amy L. Dzierba, PharmD	None	N/A
Robert W. Eisinger, PhD	None	N/A

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

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

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

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

Therapeutics and COVID-19

LIVING GUIDELINE
31 MARCH 2021



World Health
Organization



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1. Summary: what is this living guideline?

Clinical question: What is the role of drugs in the treatment of patients with COVID-19?

Target audience: The target audiences are clinicians and health care decision-makers.

Current practice: The evidence base for therapeutics for COVID-19 is increasing rapidly, and some treatments of proven benefit have emerged. Numerous randomized trials of many drugs are underway to further inform practice. This version of the WHO living guideline contains new information and a recommendation on ivermectin (1). Increased international attention on ivermectin as a potential treatment for COVID-19 triggered this recommendation.

Recommendations: In this update, the panel makes a recommendation not to use ivermectin in patients with COVID-19 except in the context of a clinical trial. Previous recommendations include:

- a strong recommendation for systemic corticosteroids in patients with severe and critical COVID-19;
- a conditional recommendation against systemic corticosteroids in patients with non-severe COVID-19;
- a conditional recommendation against remdesivir in hospitalized patients with COVID-19;
- a strong recommendation against hydroxychloroquine in patients with COVID-19 of any severity;
- a strong recommendation against lopinavir/ritonavir in patients with COVID-19 of any severity.

How this guideline was created: This living guideline represents an innovation from the World Health Organization (WHO), driven by the urgent need for global collaboration to provide trustworthy and evolving COVID-19 guidance informing policy and practice worldwide. WHO has partnered with the non-profit Magic Evidence Ecosystem Foundation (MAGIC) for methodologic support and development and dissemination of living guidance for COVID-19 drugs to prevent and treat COVID-19. These guidelines are also published in the BMJ (2), supported by two living systematic reviews with network analysis that inform the recommendations (3, 4). An international Guideline Development Group (GDG) of content experts, clinicians, patients, ethicists and methodologists produced recommendations following standards for trustworthy guideline development using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. No conflict of interest was identified for any panel member or other contributors to the guideline development process.

The latest evidence: Results from a living systematic review and network meta-analysis (NMA) that pooled data from 16 randomized controlled trials (RCTs) with 2407 participants, including both inpatients and outpatients with COVID-19, informed the recommendation on ivermectin (3). The effects of ivermectin on mortality, need for invasive mechanical ventilation, hospital admission, duration of hospitalization and time to viral clearance all remain very uncertain (all very low certainty evidence). The uncertainty results from important concerns related to risk of bias in the included studies, and imprecision from a very low number of events and, in some cases, wide confidence intervals (CIs) in pooled estimates.

Ivermectin may increase the risk of serious adverse events (SAEs) leading to drug discontinuation (odds ratio [OR] 3.07; 95% CI: 0.77–12.09; low certainty evidence) and may have little or no impact on time to clinical improvement (mean difference [MD] 0.5 fewer days; 95% CI: 1.7 fewer days to 1.1 more days; low certainty evidence). There was no credible subgroup effect based on dose. Subgroup analyses were not performed examining between-study differences in age or illness severity as per our pre-defined decision to limit subgroup analysis to within-study comparisons.

Understanding the recommendations: When moving from evidence to the recommendation not to use ivermectin except in the context of a clinical trial, the panel emphasized the large degree of uncertainty in the evidence on mortality, need for mechanical ventilation, need for hospital admission, time to clinical improvement, and other patient-important outcomes. There remains potential for harms with an increased risk of adverse events leading to study drug discontinuation. The panel believed that most well-informed patients would be reluctant to use a medication for which the evidence left high uncertainty regarding effects. The panel considered contextual factors such as resources, feasibility, acceptability, and equity for countries and health care systems were unlikely to alter the recommendation.

Info Box

This WHO *Therapeutics and COVID-19: living guideline* now includes a recommendation not to use ivermectin except in the context of a clinical trial. The guideline was initiated in response to international attention on ivermectin as a potential treatment for COVID-19. The section text provides an executive summary of the guidance. The [first version](#) of the living WHO guideline, published 2 September 2020, provides recommendations for corticosteroids (5); the [second version](#) published 20 November 2020 provides recommendations for remdesivir (6); the [third version](#) published 12 December 2020 provides recommendations for hydroxychloroquine and lopinavir/ritonavir (7). This update does not include changes for any of these drugs.

This living guideline will incorporate new recommendations on other therapies for COVID-19 and updates on existing recommendations. The guideline is therefore written, disseminated, and updated here in MAGICapp, with a user-friendly format and easy to navigate structure that accommodates dynamically updated evidence and recommendations, focusing on what is new while keeping existing recommendations within the guideline.

Please visit the [WHO website](#) for the latest version of the guidance (1), also available in the BMJ as [Rapid Recommendations](#) (2), together with the [living network meta-analysis \(LNMA\)](#) (3), a major evidence source for the guidelines. The updated LNMA informing the recommendation on ivermectin has been published in the BMJ, with the updated guideline in the BMJ pending (3).

2. Abbreviations

ALT	alanine aminotransferase
ARDS	acute respiratory distress syndrome
CAP	community-acquired pneumonia
CI	confidence interval
COVID-19	coronavirus disease 2019
eGFR	estimated glomerular filtration rate
GDG	guideline development group
GI	gastrointestinal
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRC	guideline review committee
LNMA	living network meta-analysis
MAGIC	Magic Evidence Ecosystem Foundation
MD	mean difference
NMA	network meta-analysis
OIS	optimal information size
PICO	population, intervention, comparator, outcome
PMA	prospective meta-analysis
RCT	randomized controlled trial
RR	relative risk/risk ratio
SAE	serious adverse event
WHO	World Health Organization

3. Background

As of 20 March 2021, over 121 million people worldwide have been diagnosed with COVID-19, according to the WHO dashboard (8). The pandemic has thus far claimed more than 2.6 million lives, and although some areas of the world are seeing a drop in case counts, other areas are experiencing a resurgence in cases. Vaccination is beginning to have a substantial impact on case numbers and hospitalizations in a few countries, but limitations in global access to vaccines mean that many populations remain vulnerable (9). Even in vaccinated individuals, uncertainties remain about duration of protection and efficacy of current vaccines against emerging SARS-CoV-2 variants. Taken together, there remains a need for more effective treatments for COVID-19. The COVID-19 pandemic – and the explosion of both research and misinformation – has highlighted the need for trustworthy, accessible and regularly updated living guidance to place emerging findings into context and provide clear recommendations for clinical practice (10).

This living guideline responds to emerging evidence from randomized controlled trials (RCTs) on existing and new drug treatments for COVID-19. More than 3800 trials investigating interventions for COVID-19 have been registered or are ongoing (see Section 8 – emerging evidence) (11). Among these are national and international platform trials (e.g. RECOVERY, WHO SOLIDARITY, DISCOVERY, REMAP-CAP and ACTIV) that recruit large numbers of patients in many countries, with a pragmatic and adaptive design (12, 13). These platform trials are currently investigating and reporting on interventions, including antiviral monoclonal antibodies and immunomodulators. This rapidly evolving evidence landscape requires trustworthy interpretation and expeditious clinical practice guidelines to inform clinicians and health care decision-makers.

3.1 What triggered this version of the guideline?

This fourth version of the WHO living guideline addresses the use of ivermectin in patients with COVID-19. It follows the increased international attention on ivermectin as a potential therapeutic option. While ivermectin is also being investigated for prophylaxis, this guideline only addresses its role in the treatment of COVID-19. Ivermectin is relatively inexpensive and accessible, and some countries have already witnessed its widespread use in the treatment of COVID-19; in other countries, there is increasing pressure to do so (14).

In response to this international attention, the WHO GDG now provides recommendations on ivermectin for treatment of COVID-19. Ivermectin is an antiparasitic agent that interferes with nerve and muscle function of helminths through binding glutamate-gated chloride channels (15). We currently lack persuasive evidence of a mechanism of action for ivermectin in COVID-19, and any observed clinical benefit would be unexplained (see Section 5).

3.2 Who made this guideline

WHO selected GDG members that represent all WHO regions, has equal gender balance and includes specialists in infectious diseases, pulmonary medicine, intensive care, emergency care, primary care, ethics and four patient panel members, headed by a clinical chair (Dr Michael Jacobs) and a methods chair (Dr Bram Rochweg). Declaration of interest forms were collected, assessed and managed by the WHO secretariat according to WHO standard procedures. No panel members were assessed to have a conflict of interest. GDG member bios can be found on the [WHO website](#). Evidence summaries were prepared by the systematic review team (see Section 9). Methodologic support, with high-level expertise in GRADE, was provided by the MAGIC Evidence Ecosystem Foundation (MAGIC) (see Section 9). The methodological experts were not involved in the formulation of recommendations.

3.3 How to use this guideline

This is a living guideline from WHO. The guideline is written, disseminated and updated in MAGICapp, with a format and structure that ensures user-friendliness and ease of navigation (16). It accommodates dynamic updating of evidence and recommendations that can focus on what is new while keeping existing recommendations, as appropriate, within the guideline. Section 4 outlines key methodological aspects of the living guideline process. In addition, the methodologic support team (MAGIC), under the coordination of the Guideline Collaboration Committee (see Section 9), worked with the BMJ to coordinate the simultaneous scientific publication of the living WHO guidelines (2).

The guideline is available here in MAGICapp in online, multilayered formats and via:

- [WHO website in PDF format](#)
- [WHO Academy app](#)

- [BMJ Rapid Recommendations \(2\)](#)

The purpose of the MAGICapp online formats and additional tools, such as the infographics, is to make it easier to navigate and make use of the guideline in busy clinical practice. The online multilayered formats are designed to allow end-users to find recommendations first and then drill down to find supporting evidence and other information pertinent to applying the recommendations in practice, including tools for shared decision-making ([clinical encounter decision aids](#)) (16).

4. Methods: how this guideline was created

The team developed this living WHO guideline according to standards and methods for trustworthy guidelines, making use of an innovative process to achieve efficiency in dynamic updating of recommendations (1). The methods are aligned with the [WHO Handbook for guideline development](#) and according to a pre-approved protocol (planning proposal) by the Guideline Review Committee (18).

Related guidelines

This living WHO guidance for COVID-19 treatments will be related to the larger, more comprehensive guidance for [Clinical management of COVID-19: interim guidance](#), which has a wider scope of content and has been updated and is available on MAGICapp (17). The first three WHO living guidelines, addressing corticosteroids (5), remdesivir (6), hydroxychloroquine and lopinavir/ritonavir (7), were disseminated via the WHO website, BMJ and MAGICapp.

Timing

This guidance will be living: dynamically updated and globally disseminated once new evidence warrants a change in recommendations (19). The aim is for a timeframe from trials that trigger guideline development process to WHO publication within one month, while maintaining standards for trustworthy guidelines (WHO Handbook of guideline development) (18, 19).

Stepwise approach

Here we outline the approach, involving simultaneous processes, taken to improve efficiency and timeliness of development and dissemination of living, trustworthy guidance.

Step 1: Evidence monitoring and mapping and triggering of evidence synthesis

Comprehensive daily monitoring of all emerging RCTs occurs on a continuous basis, within the context of the living systematic review and NMA, using experienced information specialists, who review all relevant information sources for new RCTs addressing interventions for COVID-19. Once practice-changing evidence, or increasing international interest, are identified, the WHO Therapeutics Steering Committee triggers the guideline development process. The trigger for producing or updating specific recommendations is based on the following (any of the three may initiate a recommendation):

- likelihood to change practice;
- sufficient RCT data on therapeutics to inform the high-quality evidence synthesis living systematic review;
- relevance to a global audience.

Step 2: Convening the GDG

The pre-selected expert panel (see Section 9) convened on two occasions to address this drug. The first meeting, held 4 February 2021, reviewed the basics of GRADE methodology including formulating population, intervention, comparator, outcome (PICO) questions and subgroups of interests, and prioritization of patient-important outcomes. At this meeting the panel finalized the PICOs and pre-specified subgroups of interest. Subsequent to the meeting, the panel participated, through email correspondence, in an outcome prioritization exercise. At the second meeting, held on 4 March 2021, the GDG panel reviewed evidence summaries, including pre-specified subgroup analysis, and a recommendation was drafted.

Step 3: Evidence synthesis

The living systematic review/NMA team, as requested by the WHO Therapeutics Steering Committee, performed an independent systematic review to examine the benefits and harms of the intervention. The systematic review team includes systematic review experts, clinical experts, clinical epidemiologists and biostatisticians. Team members have expertise in GRADE methodology and rating certainty of evidence specifically in NMAs. The NMA team considered deliberations from the initial GDG meeting, specifically focusing on the outcomes and subgroups prioritized by the panel. To conduct the subgroup analysis of high versus low dose of ivermectin, Professor Andrew Owen (see Section 9), provided direction on analysis of different dosing regimens. Based on pharmacokinetic data, Professor Owen and the methods support team recommended analysing cumulative dose as a continuous variable, further adding a co-variate for single vs multiple dosing regimens. This subgroup analysis informed the direct comparison of ivermectin compared with standard of care only, and not the network analysis.

Step 4: Final recommendations

The GRADE approach provided the framework for establishing evidence certainty and generating both the direction and strength of recommendations (20, 21). While a priori voting rules informed procedures if the panel failed to reach consensus, these procedures proved unnecessary for this recommendation.

The following key factors informed transparent and trustworthy recommendations.

- absolute benefits and harms for all patient-important outcomes through structured evidence summaries (e.g. GRADE summary of findings tables) (22);
- quality/certainty of the evidence (20, 23);
- values and preferences of patients (24);
- resources and other considerations (including considerations of feasibility, applicability, equity) (24);
- effect estimates and confidence intervals for each outcome, with an associated rating of certainty in the evidence, as presented in summary of findings tables. If such data are not available, the panel reviews narrative summaries;
- recommendations are rated as either conditional or strong, as defined by GRADE. If the panel members disagree regarding the evidence assessment or strength of recommendations, WHO will apply voting according to established rules.

Step 5: External and internal review

The WHO guideline was reviewed by pre-specified external reviewers (see Section 9) and approved by the WHO Guideline Review Committee (GRC).

5. The latest evidence

This section outlines what information the GDG panel requested and used in making their recommendation for ivermectin.

Mechanism of action

Based on *in vitro* experiments, some have postulated that ivermectin may have a direct antiviral effect against SARS-CoV-2. However, in humans the concentrations needed for *in vitro* inhibition are unlikely to be achieved by the doses proposed for COVID-19 (25-27). Ivermectin had no impact on SARS-CoV-2 viral RNA in the Syrian golden hamster model of SARS-CoV-2 infection (28). The proposed mechanism remains unclear: multiple targets have been proposed based upon either analogy to other viruses with very different life cycles, or, like several hundred other candidates, simulations indicating molecular docking with multiple viral targets including spike, RdRp and 3CLpro (29-33). No direct evidence for any mechanism of antiviral action against SARS-CoV-2 currently exists.

Some have proposed, based predominantly upon research in other indications, that ivermectin has an immunomodulatory effect, but again the mechanism remains unclear. Historical data showed that ivermectin improved survival in mice given a lethal dose of lipopolysaccharide (34), and has benefits in murine models of atopic dermatitis and allergic asthma (35, 36). For SARS-CoV-2, one hypothesis suggests immunomodulation mediated by allosteric modulation of the alpha-7 nicotinic acetylcholine receptor (indirectly by modulating the activity of ligands of the receptor). Although investigators have demonstrated this action *in vitro*, concentrations used in these experiments have been even higher than those required for an antiviral effect (37), and therefore very unlikely to be achieved in humans. In the Syrian golden hamster model of SARS-CoV-2 infection, ivermectin resulted in some changes in pulmonary immune phenotype consistent with allosteric modulation of the alpha-7 nicotinic acetylcholine receptor (28). However, ivermectin did not appear to rescue body weight loss which is a hallmark of disease in this model, and drug concentrations were not measured to extrapolate to those achieved in humans. Taken together, there remains great uncertainty regarding the relevance of any immunomodulatory or anti-inflammatory action of ivermectin.

Benefits and harms

The GDG members prioritized outcomes (rating from 1 [not important] to 9 [critical]) taking a patient's perspective. The panel prioritized outcomes from both an inpatient (Table 1) and outpatient (Table 2) perspective. The panel's questions were structured using the PICO format (see evidence profile under the recommendations). These prioritized outcomes were used to update the LNMA.

Table 1. Panel outcome rating from an inpatient perspective

Outcome	Mean	SD	Range
Death	9.0	0.0	9
Need for invasive mechanical ventilation	8.2	0.9	6-9
Duration of invasive mechanical ventilation	7.6	0.9	6-9
Quality of life	6.9	1.3	5-9
Duration of hospitalization	6.7	1.2	4-9
Serious adverse effects (e.g. adverse events leading to drug discontinuation)	6.7	1.8	3-9
Time to symptom resolution	6.5	1.6	4-9
New non-SARS-CoV2 infection	6.4	1.8	3-9
Duration of oxygen support	6.3	1.3	4-9
Time to viral clearance	4.7	2.3	1-9

SD: standard deviation.

Note: 1: not important, 9: critically important.

Table 2. Panel outcome rating from an outpatient perspective

Outcome	Mean	SD	Range
Admission to hospital	8.5	0.7	7-9
Death	8.1	1.9	3-9
Quality of life	7.5	1.3	5-9
Serious adverse effects (e.g. adverse events leading to drug discontinuation)	7.4	1.8	3-9
Time to symptom resolution	7.3	1.7	4-9
Duration of hospitalization	6.6	0.9	5-8
Duration of oxygen support	6.6	1.2	5-9
Need for invasive mechanical ventilation	5.9	2.3	1-8
New non-SARS-CoV2 infection	5.6	2.1	3-9
Time to viral clearance	5.5	2.4	1-9
Duration of invasive mechanical ventilation	5.4	2.1	1-8

SD: standard deviation.

Note: 1: not important, 9: critically important.

Evidence summary

The evidence summary was based on 16 trials and 2407 participants for which the NMA provided relative estimates of effect for patient-important outcomes. Of the included trials, 75% examined patients with non-severe disease and 25% included both severe and non-severe patients. A number of the included trials did not report on our outcomes of interest. Of the trials, 25% were published in peer-reviewed journals, 44% were available as preprints and 31% were completed but unpublished (See [Table on trial characteristics](#)). We excluded a number of quasi-RCTs (38-41).

Subgroup analysis

The NMA team performed subgroup analyses which could result in distinct recommendations by subgroups. From the available data, subgroup analyses were only possible by dose of ivermectin and considering the outcomes of mortality, mechanical ventilation, admission to hospital, and adverse events leading to drug discontinuation. The ivermectin dose subgroup analyses were performed from the direct comparison of ivermectin versus usual care. For these analyses, meta-regression was used to evaluate the effect of cumulative dose as a continuous variable, and further adding a co-variate for single vs multiple dosing regimens. This approach was based on input from the pharmacology experts (led by Professor Andrew Owen) who performed pharmacokinetic simulations across trial doses, and found that cumulative ivermectin dose was expected to correlate with key pharmacokinetic parameters when single- and multiple-dose studies were segregated. It should be noted that the included trials did not directly assess the pharmacokinetics of ivermectin, and our approach was based upon simulations validated where possible against published pharmacokinetics in humans. The panel used a pre-specified framework incorporating the ICEMAN tool to assess the credibility of subgroup findings (42).

The GDG panel requested subgroup analyses based on: age (considering children vs younger adults vs older adults [70 years or older]); illness severity (non-severe vs severe vs critical COVID-19); time from onset of symptoms; and use of concomitant medications. However, there was insufficient within-trial data to perform any of these subgroup analyses, based on our pre-specified protocol. The panel recognized that usual care is likely variable between centres and regions, and has evolved over time. However, given all of the data come from RCTs, use of these co-interventions that comprise usual care should be balanced between study patients randomized to either the intervention or usual care arms.

Baseline risk estimates (prognosis of patients with COVID-19): informing absolute estimates of effect

The evidence summaries that informed the guideline recommendation reported the anticipated absolute effects of ivermectin compared with usual care across all patient-important outcomes. The absolute effects of treatment are informed by the prognosis (i.e. baseline risk estimates) combined with the relative estimates of effects (e.g. risk ratios [RR], OR) obtained from the NMA.

The control arm of the WHO SOLIDARITY trial (13), performed across a wide variety of countries and geographical regions, was identified by the GDG panel as generally representing the most relevant source of evidence for baseline risk estimates for mortality and mechanical ventilation. The rationale for selecting the WHO SOLIDARITY trial was to reflect the overall prognosis of the global population for which the WHO guideline recommendations are made. However, the SOLIDARITY trial only enrolls patients who are hospitalized with COVID-19. Since ivermectin has been proposed for use and often studied in outpatients, on this occasion the panel used the median of risk in the standard care arms of the included trials for baseline risk estimates for these outcomes. When applying the evidence to a particular patient or setting, for any medication with a convincing effect, clinicians should consider the individual's risk of mortality and need for mechanical ventilation. In view of the study designs, the GDG judged that for other outcomes using the median or mean of all patients randomized to usual care across the included studies would provide the most reliable estimate of baseline risk.

Values and preferences

We had insufficient information to provide the GDG with a trustworthy description of patients' experiences or values and preferences regarding treatment decisions for COVID-19 drug treatments. The GDG therefore relied on their own judgments of what well-informed patients would value after carefully balancing the benefits, harms and burdens of treatment. The GDG included four patient-partners who had lived experience with COVID-19.

The GDG agreed that the following values and preferences would be typical of well-informed patients:

- Most patients would be reluctant to use a medication for which the evidence left high uncertainty regarding effects on outcomes they consider important. This was particularly so when evidence suggested treatment effects, if they do exist, are small, and the possibility of important harm remains.
- In an alternative situation with larger benefits and less uncertainty regarding both benefits and harms, more patients would be inclined to choose the intervention.

Although the GDG focused on an individual patient perspective, they also considered a population perspective in which feasibility, acceptability, equity and cost are important considerations.

6. Who do the recommendations apply to?

Info Box

The guideline for COVID-19 therapeutics applies to all patients with COVID-19. For some drugs (such as corticosteroids), recommendations may differ based on the severity of COVID-19 disease. The GDG used the WHO severity definitions based on clinical indicators, adapted from WHO COVID-19 disease severity categorization (see below) (17). These definitions avoid reliance on access to health care to define patient subgroups.

WHO Severity definitions

- **Critical COVID-19** – Defined by the criteria for acute respiratory distress syndrome (ARDS), sepsis, septic shock, or other conditions that would normally require the provision of life-sustaining therapies such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy.
- **Severe COVID-19** – Defined by any of:
 - Oxygen saturation <90% on room air;
 - Respiratory rate > 30 breaths/min in adults and children > 5 years old; ≥ 60 breaths/min in children < 2 months old; ≥ 50 in children 2–11 months old; and ≥ 40 in children 1–5 years old;
 - Signs of severe respiratory distress (accessory muscle use, inability to complete full sentences, and, in children, very severe chest wall indrawing, grunting, central cyanosis, or presence of any other general danger signs).
- **Non-severe COVID-19** – Defined as absence of any criteria for severe or critical COVID-19.

Caution: The panel noted that the oxygen saturation threshold of 90% to define severe COVID-19 was arbitrary and should be interpreted cautiously when used to define disease severity. For example, clinicians must use their judgment to determine whether a low oxygen saturation is a sign of severity or is normal for a given patient with chronic lung disease. Similarly, a saturation > 90–94% on room air is abnormal (in patient with normal lungs) and can be an early sign of severe disease, if patient is on a downward trend. Generally, if there is any doubt, the panel suggested erring on the side of considering the illness as severe.

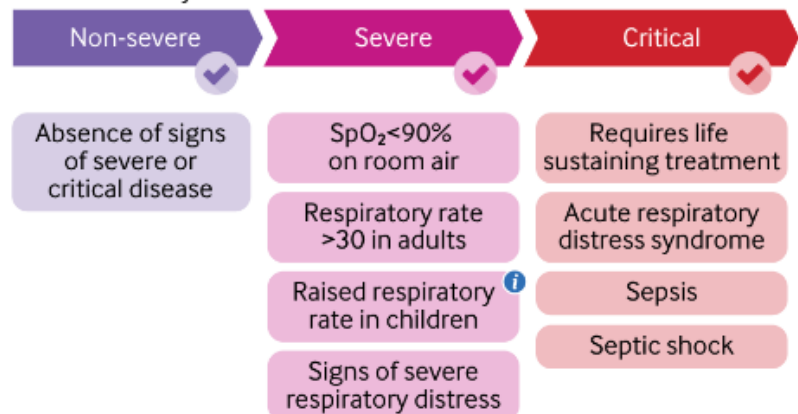
The infographic illustrates these three disease severity groups and key characteristics to apply in practice.

Population

This recommendation applies only to people with these characteristics:



Disease severity



Infographic co-produced by BMJ and MAGIC; designer Will Stahl-Timmins (see [BMJ Rapid Recommendations](#)).

7. Recommendations for therapeutics

7.1 Ivermectin

Only in research settings

New

We recommend not to use ivermectin in patients with COVID-19 except in the context of a clinical trial.

Remark: This recommendation applies to patients with any disease severity and any duration of symptoms.

A recommendation to only use a drug in the setting of a clinical trials is appropriate when there is very low certainty evidence and future research has a large potential for reducing uncertainty about the effects of the intervention and for doing so at reasonable cost.

Practical info

The GDG made a recommendation against using ivermectin for treatment of patients with COVID-19 outside the setting of a clinical trial and therefore practical considerations are less relevant for this drug.

Evidence to decision

Benefits and harms

The effects of ivermectin on mortality, mechanical ventilation, hospital admission, duration of hospitalization and viral clearance remain uncertain because of very low certainty of evidence addressing each of these outcomes. Ivermectin may have little or no effect on time to clinical improvement (low certainty evidence). Ivermectin may increase the risk of SAEs leading to drug discontinuation (low certainty evidence).

Subgroup analyses indicated no effect modification based on dose. We were unable to examine subgroups based on patient age or severity of illness due to insufficient trial data (see Section 5). Therefore, we assumed similar effects in all subgroups. This recommendation applies to patients with any disease severity and any duration of symptoms.

Certainty of the evidence

For most key outcomes, including mortality, mechanical ventilation, hospital admission, duration of hospitalization and viral clearance, the panel considered the evidence of very low certainty. Evidence was rated as very low certainty primarily because of very serious imprecision for most outcomes: the aggregate data had wide confidence intervals and/or very few events. There were also serious concerns related to risk of bias for some outcomes, specifically lack of blinding, lack of trial pre-registration, and lack of outcome reporting for one trial that did not report mechanical ventilation despite pre-specifying it in their protocol (publication bias).

For more details, see the Justification section for this recommendation. For other outcomes, including SAEs and time to clinical improvement, the certainty of the evidence was low.

Preference and values

Applying the agreed values and preferences (see Section 5), the GDG inferred that almost all well-informed patients would want to receive ivermectin only in the context of a randomized trial, given that the evidence left a very high degree of uncertainty in effect on mortality, need for mechanical ventilation, need for hospitalization and other critical outcomes of interest and there was a possibility of harms, such as treatment-associated SAEs. The panel anticipated little variation in values and preferences between patients when it came to this intervention.

Resources and other considerations

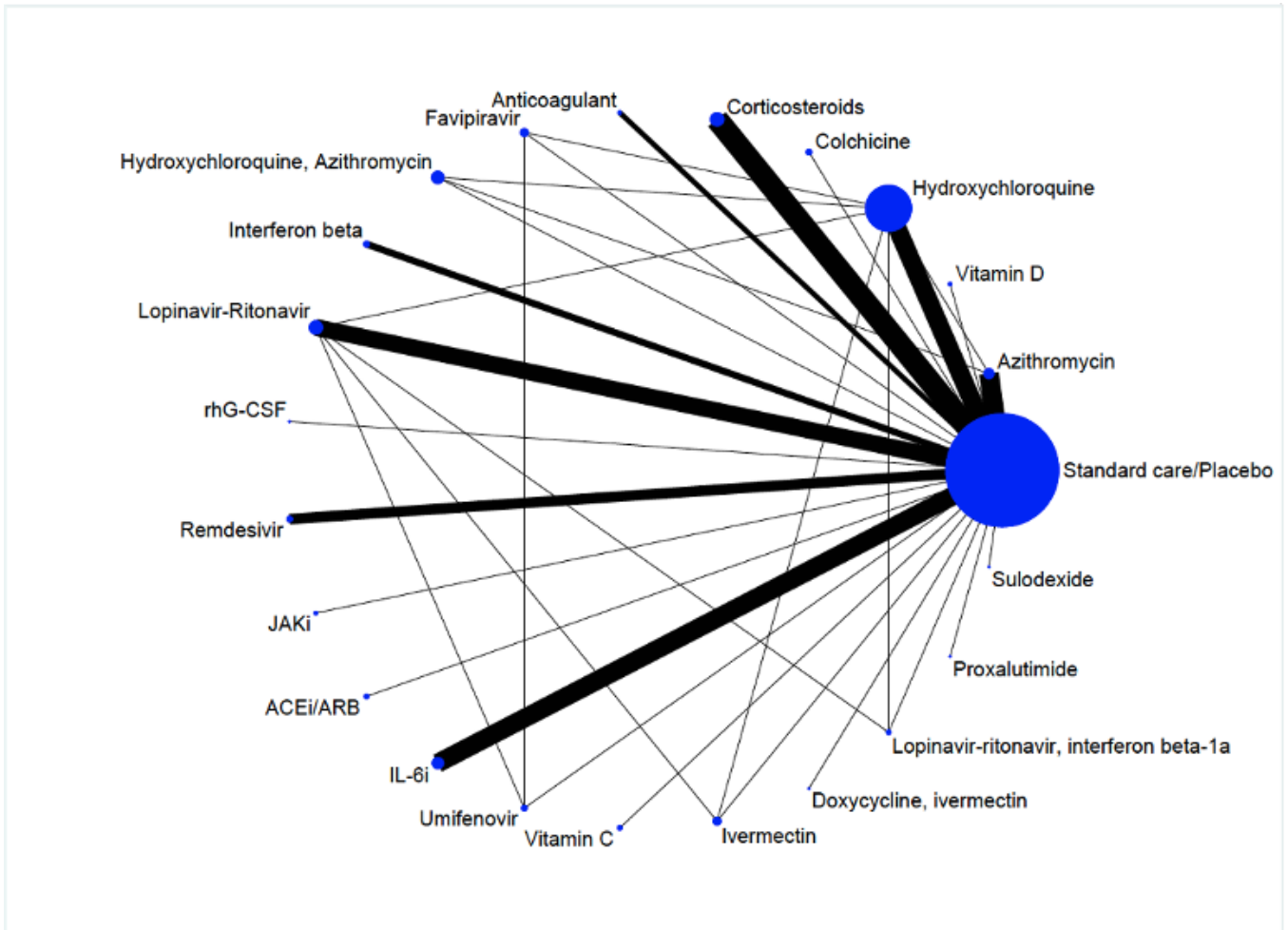
Ivermectin is a relatively inexpensive drug and is widely available, including in low-income settings. The low cost and wide availability do not, in the panel's view, mandate the use of a drug in which any benefit remains very uncertain and ongoing concerns regarding harms remain. Although the cost may be low per patient, the GDG panel raised concerns about diverting attention and resources away from care likely to provide a benefit such as corticosteroids in patients with severe COVID-19 and other supportive care interventions. Also, use of ivermectin for COVID-19 would divert drug supply away from pathologies for which it is clearly indicated, potentially contributing to drug shortages, especially for helminth control and elimination programmes. Other endemic infections that may worsen with corticosteroids should be considered. If steroids are used in the treatment of COVID-19, empiric treatment with ivermectin may still be considered in Strongyloidiasis endemic areas, at the discretion of clinicians overseeing treatment, albeit not for treatment of COVID-19 itself.

Justification

When moving from evidence to a recommendation on the use of ivermectin in patients with COVID-19 only in the context of a clinical trial, the panel emphasized the high degree of uncertainty in the most critical outcomes such as mortality and need for mechanical ventilation. It also noted the evidence suggesting possible harm associated with treatment, with increased adverse events. The GDG did not anticipate important variability in patient values and preferences. Other contextual factors, such as resource considerations, accessibility, feasibility and impact on health equity did not alter the recommendation.

Compared with previous drugs evaluated as part of the WHO Living Guidelines for Therapeutics in COVID-19 (see below), currently there are far fewer RCT data available for ivermectin. The existing data on ivermectin also have a substantially higher degree of uncertainty, with included trials having enrolled substantially fewer patients with far fewer events. Fig. 1 is the network map for mortality from the accompanying LNMA informing this guideline. Within the map, the size of the nodes (blue circles) correlates with the number of patients randomized to that intervention across all included trials; it is clear that the size of the ivermectin node is much smaller than other interventions which have been subjected to WHO guidelines, such as corticosteroids, hydroxychloroquine and lopinavir/ritonavir. The width of the line connecting two specific interventions correlates with the number of patients and number of events in this comparison across all trials; again, the lines connecting ivermectin to standard of care, as well as to the comparators lopinavir/ritonavir and hydroxychloroquine, are much thinner compared with drugs that have been assessed previously in this guideline.

Fig. 1. Network map from the living network meta-analysis informing this guideline

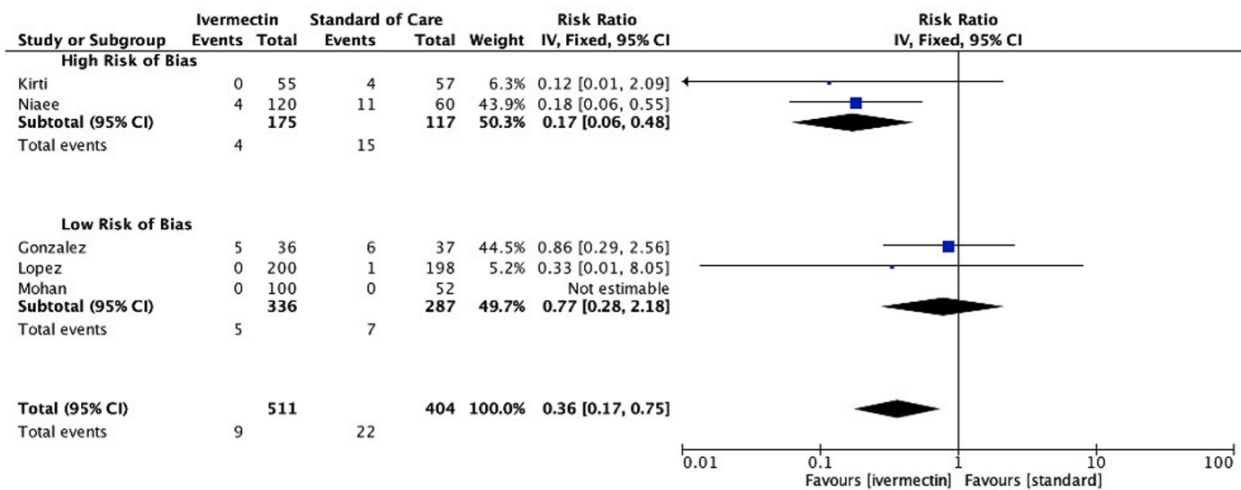


Drugs for which this guideline has already addressed with recommendations include corticosteroids, remdesivir, hydroxychloroquine and lopinavir/ritonavir.

High degree of uncertainty

The certainty in effect estimates for ivermectin on the main outcomes of interest, including mortality, is very low and therefore the effect of ivermectin on these outcomes remains uncertain. There are two domains that contribute to this uncertainty: serious risk of bias; and serious imprecision. Although 16 RCTs contributed to the evidence summary informing this drug, only five directly compared ivermectin with standard of care and reported mortality (43-47). Of note, and in keeping with our methodology, the LNMA team excluded quasi-randomized trials, or any RCT that did not use explicit randomization techniques. Of these five RCTs, two (43, 44) were at high risk of bias, due to inadequate blinding. One of these two trials (43) also started enrolling and randomizing patients prior to the protocol being publicly posted, another factor that contributes to an increased risk of bias. The potential impact of risk of bias is exemplified by subgroup analyses for mortality based on trial risk of bias. As demonstrated in the forest plot (Fig. 2), the pooled estimate across all five RCTs that directly compare ivermectin with standard care suggests a reduction in mortality with ivermectin, but this effect is not apparent if we only consider the trials at low risk of bias (which together contribute nearly two-thirds of the evidence). This finding increases the degree of uncertainty regarding the true effect of ivermectin on mortality. Consistent with the direct evidence, a similar phenomenon is observed with the indirect evidence comparing ivermectin to standard of care (via comparisons against hydroxychloroquine and lopinavir/ritonavir). The indirect evidence suggesting a reduction in mortality with ivermectin is driven almost entirely by one study which is at high risk of bias (48) due to a lack of detailed description of blinding or randomization and the lack of a publicly available study protocol (figure not shown).

Fig. 2. Forest plot demonstrating direct comparison of ivermectin versus standard of care for mortality with subgroup analysis by risk of bias



IV: inverse variance.

In addition to concerns related to risk of bias, for the outcome of mortality, there are very serious concerns related to imprecision. According to GRADE, imprecision is evaluated based on both a confidence interval approach and an evaluation of information size (event number), ensuring there is adequate information on which to make informed judgments (49). In this case, despite confidence intervals that suggest benefit with ivermectin, the information size is very low. For mortality (and ignoring the concerns related to risk of bias discussed above), there were nine deaths across all 511 patients randomized to ivermectin (1.76%) and 22 deaths across all 404 patients randomized to standard of care (5.45%). This is an extremely small number of events on which to base conclusions, and far below the optimal information size. In fact, performing a theoretical exercise in which a change of three events (deaths) is made from those randomized to standard of care to those randomized to ivermectin eliminates any statistical significance, a finding that suggests that results could reasonably be due to chance alone. Furthermore, the evidence informing this comparison is from multiple small trials, adding to the risk of unrecognized imbalances in study arms. Given the strong likelihood that chance may be playing a role in the observed findings, the panel believed there was very serious imprecision further lowering the overall certainty in findings.

This combination of serious risk of bias and very serious imprecision contributed to very low certainty of evidence for mortality despite a point estimate and confidence interval that appear to suggest benefit with ivermectin. As a result, the panel concluded that the effect of ivermectin on mortality is uncertain. Similar considerations were applied to the other critical outcomes including mechanical ventilation, hospital admission, and duration of hospitalization and resulted in very low certainty for these outcomes as well.

Subgroup analyses

We conducted subgroup analysis only for effect by ivermectin dose and the panel did not find any evidence of a subgroup effect (see Section 5). A lack of within-trial comparisons prevented subgroup analyses by age or disease severity. Therefore, the panel did not make any subgroup recommendation for this drug. In other words, the recommendation against ivermectin except in the context of clinical trials is applicable across disease severity, age groups, and all dose regimens of ivermectin.

Applicability

None of the included RCTs enrolled children under 15, and therefore the applicability of this recommendation to children is currently uncertain. However, the panel had no reason to think that children with COVID-19 would respond any differently to treatment with ivermectin. There were similar considerations for pregnant women, with no data directly examining this population, but no rationale to suggest they would respond differently to other adults.

Uncertainties

Please see end of document for residual uncertainties (Section 8).

Clinical question/ PICO

Population: Patients with COVID-19 infection (all disease severities)
Intervention: Ivermectin
Comparator: Usual care

Summary

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Plain text summary
		Standard care	Ivermectin		
Mortality	Odds ratio 0.19 (CI 95% 0.09 - 0.36) Based on data from 1,419 patients in 7 studies. ¹ (Randomized controlled)	70 per 1000	14 per 1000	Very Low Due to serious risk of bias and very serious imprecision ²	The effect of ivermectin on mortality is uncertain.
Mechanical ventilation	Odds ratio 0.51 (CI 95% 0.12 - 1.77) Based on data from 687 patients in 5 studies. (Randomized controlled)	20 per 1000	10 per 1000	Very Low Due to very serious imprecision and publication bias ³	The effect of ivermectin on mechanical ventilation is uncertain.
Viral clearance 7 days	Odds ratio 1.62 (CI 95% 0.95 - 2.86) Based on data from 625 patients in 6 studies. (Randomized controlled)	500 per 1000	618 per 1000	Low Due to serious inconsistency and imprecision ⁴	Ivermectin may increase or have no effect on viral clearance.
Hospital admission (outpatients only)	Odds ratio 0.36 (CI 95% 0.08 - 1.48) Based on data from 398 patients in 1 studies. (Randomized controlled)	50 per 1000	18 per 1000	Very Low Due to extreme imprecision ⁵	The effect of ivermectin on hospital admission is uncertain.
Serious adverse events	Odds ratio 3.07 (CI 95% 0.77 - 12.09) Based on data from 584 patients in 3 studies. (Randomized controlled)	9 per 1000	27 per 1000	Low Due to very serious imprecision ⁶	Ivermectin may increase the risk of serious adverse events leading to drug discontinuation.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Plain text summary
		Standard care	Ivermectin		
Time to clinical improvement	Measured by: days Lower better Based on data from: 633 patients in 2 studies. (Randomized controlled)	11 days (Mean)	10.5 days (Mean)	Low Due to very serious imprecision ⁷	Ivermectin may have little or no difference on time to clinical improvement
Duration of hospitalization	Measured by: days Lower better Based on data from: 252 patients in 3 studies. (Randomized controlled)	12.8 days (Mean)	11.7 days (Mean)	Very Low Due to serious imprecision, inconsistency and serious risk of bias ⁸	The effect of ivermectin on hospital length of stay is uncertain.
Time to viral clearance	Measured by: days Lower better Based on data from: 559 patients in 4 studies. (Randomized controlled)	7.3 days (Mean)	5.7 days (Mean)	Very Low Due to very serious imprecision and serious risk of bias. ⁹	We are uncertain whether ivermectin improves or worsen time to viral clearance

1. Systematic review (3). **Baseline/comparator:** Control arm of reference used for intervention. We elected to use the control arm of the WHO solidarity trial, reflecting usual care across countries participating in the trial.
2. **Risk of bias: Serious.** The large trial contributing most of the effect estimate was driven by studies that were not blinded.. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** The number of total events was very small.. **Publication bias: No serious.**
3. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Very few events and credible intervals that include both important benefit and harm.. **Publication bias: Serious.**
4. **Inconsistency: Serious.** The point estimates varied widely and credible intervals do not substantially overlap.. **Indirectness: No serious. Imprecision: Serious.** Credible interval includes no effect.. **Publication bias: No serious.**
5. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Credible interval includes important benefit and harm.. **Publication bias: No serious.**
6. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Credible interval includes little to no difference.. **Publication bias: No serious.**
7. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious. Publication bias: No serious.**
8. **Risk of bias: Serious.** Result driven by one study that was not blinded.. **Inconsistency: Serious.** Despite overlapping confidence intervals, point estimates discrepant.. **Indirectness: No serious. Imprecision: Serious.** Credible intervals include no difference.. **Publication bias: No serious.**
9. **Risk of bias: Serious.** Concerns around risk of bias.. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Credible interval includes important benefit and important harm.. **Publication bias: No serious.**

7.2 Hydroxychloroquine (published December 17 2020)

The third version of the WHO living guideline addressed the use of hydroxychloroquine (and lopinavir/ritonavir, see below) in patients with COVID-19. It followed the pre-print publication of the WHO SOLIDARITY trial on 15 October, 2020, reporting results on treatment with remdesivir, hydroxychloroquine and lopinavir-ritonavir in hospitalized patients with COVID-19 (50). The role of

these drugs in clinical practice has remained uncertain, with limited prior trial evidence. The WHO SOLIDARITY trial adds 11,266 randomized patients (2570 to remdesivir, 954 to hydroxychloroquine, and 1411 to lopinavir-ritonavir, 6,331 to usual care) and had the potential to change practice (13, 50).

The evidence

The evidence summary for hydroxychloroquine was based on 30 trials and 10 921 participants for which the NM provided relative estimates of effect for patient-important outcomes (Table 3). Five of the trials (414 total participants) randomized some patients to chloroquine.

Table 3. Summary of trials and trial characteristics informing the hydroxychloroquine recommendation

(trials = 30, total patients = 10 921)

Geographic region	Region of the Americas South-East Asia Region Western Pacific Region European Region Eastern Mediterranean Region	Region of the Americas (12 trials, 2358 patients) South-East Asia and Western Pacific Regions (7 trials, 731 patients) European Region (10 trials, 7638 patients) Eastern Mediterranean Region (1 trial, 194 patients)
Severity of illness ^a	Non-severe Severe Critically ill	Mild/Moderate (10 trials, 2436 patients) Severe (1 trials, 479 patients) Critically ill (0 trials, 0 patients)
Mechanically ventilated at baseline ^b	Mean (range), %	3.23 (0–16.8)
Age ^c	Mean (range of means), years	50.8 (32.9–77.0)
Sex ^d	Mean (range of means), % women	46.9 (30.0–71.0)
Loading doses Day 1 ^e	Mean (range of means), mg	1010 (800–1600)
Total cumulative doses ^f	Median (range), mg	4000 (2000–11200)
Duration of therapy ^g	Median (range), days	7 (4–16)
Type of care	n (%) inpatient n (%) outpatient	Inpatient: 9549 (87.4) Outpatient: 1372 (12.6)
Trial participants	Median (range)	364 (2–4716)
Concomitant use of corticosteroids ^h	Mean (range across trials that report this), %	12.61 (8.0–19.5)

Notes:

^a 19 trials did not report the disease severity of patients.

^b 19 trials did not report the proportion of mechanical ventilation at baseline.

^c Based on 15 trials and 8006 patients. For the other 15 trials: 1 trial did not report the age of patients; and the other 14 trials reported that the age of patients were ≥ 12 , 18 or 40.

^d 14 trials did not report the sex of patients.

^e 10 trials did not use a loading dose.

^f 1 trial reported range of treatment duration.

^g 1 trial reported range of treatment duration.

^h 23 trials did not report the concomitant use of corticosteroids.

Baseline risk

The absolute effects of treatment are informed by the prognosis (i.e. baseline risk estimates) combined with the relative estimates of effects (e.g. risk ratio, odds ratio) obtained from the NMA.

The control arm of the WHO SOLIDARITY Trial (13), performed across a wide variety of countries and geographical regions, was identified by the GDG panel as representing the most relevant source of evidence to make the baseline risk estimates for the outcomes of mortality and mechanical ventilation. The rationale for selecting the WHO SOLIDARITY Trial was to reflect the overall prognosis of the global population for which the WHO guideline recommendations are made. When applying the evidence to a particular patient or setting, the individual or setting's risk of mortality and mechanical ventilation should be considered. In view of the study designs, the GDG determined that for other outcomes using the median or mean of all patients randomized to usual care

across the included studies would provide the most reliable estimate of baseline risk.

Subgroup analysis

For hydroxychloroquine, the GDG panel requested subgroup analyses based on age (considering children vs younger adults [e.g. under 70 years] vs older adults [e.g. 70 years or older]), illness severity (non-severe vs severe vs critical COVID) and based on whether or not it was co-administered with azithromycin.

The panel also requested a subgroup analysis based on high dose vs low dose hydroxychloroquine. A categorical approach to hydroxychloroquine dosing proved impossible because the trials used varying loading doses, continuation doses and durations. Therefore, in collaboration with a pharmacology expert (Professor Andrew Owen), we modelled the expected serum concentrations over time. We hypothesized that higher trough concentrations early in the treatment course (e.g. trough concentration on Day 3) might be more effective than lower early trough concentrations. We also hypothesized that higher maximum serum concentrations (e.g. peak concentration on the last day) might result in higher risk of adverse effects than lower maximum serum concentrations. In our pharmacokinetic model, the cumulative dose was highly correlated with all measures of serum concentrations on Day 3 and the final day of treatment, and therefore we decided to use cumulative dose as the primary analysis. Day 3 trough concentration was least strongly correlated with total cumulative dose ($R^2 = 0.376$) and therefore we performed a sensitivity subgroup analysis with predicted Day 3 trough concentrations for efficacy outcomes.

Info Box

The recommendation concerning hydroxychloroquine was published December 17 2020 as the [third version](#) of the WHO living guideline and in the BMJ as [Rapid Recommendations](#). No changes were made for the hydroxychloroquine recommendation in this fourth version of the guideline. Please view the section text for a summary of the evidence requested to inform the recommendation, triggered by the WHO Solidarity trial.

Recommendation against

We recommend against administering hydroxychloroquine or chloroquine for treatment of COVID-19.

Remark: This recommendation applies to patients with any disease severity and any duration of symptoms.

Practical info

The GDG made a strong recommendation against using hydroxychloroquine or chloroquine for treatment of patients with COVID-19. The use of hydroxychloroquine may preclude the use of other important drugs that also prolong the QT interval, such as azithromycin and fluoroquinolones. Concomitant use of drugs that prolong the QT interval should be done with extreme caution.

Evidence to decision

Benefits and harms

Hydroxychloroquine and chloroquine probably do not reduce mortality or mechanical ventilation and may not reduce duration of hospitalization. The evidence does not exclude the potential for a small increased risk of death and mechanical ventilation with hydroxychloroquine. The effect on other less important outcomes, including time to symptom resolution, admission to hospital, and duration of mechanical ventilation, remains uncertain.

Hydroxychloroquine may increase the risk of diarrhoea and nausea/vomiting; a finding consistent with evidence from its use in other conditions. Diarrhoea and vomiting may increase the risk of hypovolaemia, hypotension and acute kidney injury, especially in settings where health care resources are limited. Whether or not and to what degree hydroxychloroquine

increases the risk of cardiac toxicity, including life-threatening arrhythmias, is uncertain.

Subgroup analyses indicated no effect modification based on severity of illness (comparing either critical vs severe/non-severe or non-severe vs critical/severe) or age (comparing those aged < 70 years versus those > 70 years old). Further, the cumulative dose and predicted Day 3 serum trough concentrations did not modify the effect for any outcome. Therefore, we assumed similar effects in all subgroups.

We also reviewed evidence comparing the use of hydroxychloroquine plus azithromycin vs hydroxychloroquine alone. There was no evidence that the addition of azithromycin modified the effect of hydroxychloroquine for any outcome (very low certainty).

Certainty of the evidence

For the key outcomes of mortality and mechanical ventilation, the panel considered the evidence to be of moderate certainty. There were residual concerns about lack of blinding in the largest trials and the imprecision. For example, the credible interval around the pooled effect leaves open the possibility of a very small reduction in mortality. The quality of evidence was low for diarrhoea and nausea/vomiting because of lack of blinding in many of the trials and because the total number of patients enrolled in trials reporting these outcomes was smaller than the optimal information size (although the credible interval laid entirely on the side of harm for both outcomes).

For all other outcomes, the certainty of the evidence was low or very low. The primary concerns with the data were imprecision (credible intervals included both important benefit and important harm) as well as risk of bias (lack of blinding).

Preference and values

Applying the agreed values and preferences (see Evidence section above), the GDG inferred that almost all well-informed patients would not want to receive hydroxychloroquine given the evidence suggesting there was probably no effect on mortality or need for mechanical ventilation and there was a risk of adverse events including diarrhoea and nausea and vomiting. The panel did not expect there would be much variation in values and preferences between patients when it came to this intervention.

Resources and other considerations

Hydroxychloroquine and chloroquine are relatively inexpensive compared with other drugs used for COVID-19 and are already widely available, including in low-income settings. Despite this, the panel felt that almost all patients would choose not to use hydroxychloroquine or chloroquine because the harms outweigh the benefits. Although the cost may be low per patient, the GDG panel raised concerns about diverting attention and resources away from care likely to provide a benefit such as corticosteroids in patients with severe COVID-19 and other supportive care interventions.

Justification

When moving from evidence to the strong recommendation against the use of hydroxychloroquine or chloroquine for patients with COVID-19, the panel emphasized the moderate certainty evidence of probably no reduction in mortality or need for mechanical ventilation. It also noted the evidence suggesting possible harm associated with treatment, with increased nausea and diarrhoea. The GDG did not anticipate important variability in patient values and preferences, and other contextual factors, such as resource considerations, accessibility, feasibility and impact on health equity (see summary of these factors under Evidence to decision).

Subgroup analyses

The panel did not find any evidence of a subgroup effect across patients with different levels of disease severity, between adults and older adults, and by different doses, and therefore did not make any subgroup recommendation for this drug. In other

words, the strong recommendation is applicable across disease severity, age groups, and all doses and dose schedules of hydroxychloroquine.

The trials included patients from around the world, with all disease severities, and treated in different settings (outpatient and inpatient). Although the trials did not report subgroup effects by time from symptom onset, many of the trials enrolled patients early in the disease course. The GDG panel therefore felt that the evidence applies to all patients with COVID-19.

Applicability

Special populations

None of the included RCTs enrolled children, and therefore the applicability of this recommendation to children is currently uncertain. However, the panel had no reason to think that children with COVID-19 would respond any differently to treatment with hydroxychloroquine. There were similar considerations in regards to pregnant women, with no data directly examining this population, but no rationale to suggest they would respond differently than other adults. Hydroxychloroquine crosses the placental barrier and there are concerns that it may lead to retinal damage in neonates. Although hydroxychloroquine has been used in pregnant women with systemic autoimmune diseases, such as systemic lupus erythematosus, pregnant women may have even more reasons than other patients to be reluctant to use hydroxychloroquine for COVID-19.

In combination with azithromycin

There was no evidence from the NMA that the addition of azithromycin modified the effect of hydroxychloroquine for any outcome. As there were no trial data suggesting that azithromycin favourably modifies the effect of hydroxychloroquine, the recommendation against hydroxychloroquine and chloroquine applies to patients whether or not they are concomitantly receiving azithromycin.

Uncertainties

Please see end of document for residual uncertainties (Section 8). The GDG panel felt that it was unlikely future studies would identify a subgroup of patients that are likely to benefit from hydroxychloroquine or chloroquine.

Clinical question/ PICO

- Population:** Patients with COVID-19 infection (all disease severities)
- Intervention:** Hydroxychloroquine + usual care
- Comparator:** Usual care

Summary

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Plain text summary
		Standard care	Hydroxychloroquine		
Mortality	Odds ratio 1.11 (CI 95% 0.95 - 1.31) Based on data from 10,859 patients in 29 studies. ¹ (Randomized controlled)	106 per 1000	116 per 1000	Moderate Due to borderline risk of bias and imprecision ²	Hydroxychloroquine probably does not reduce mortality.
		Difference: 10 more per 1000 (CI 95% 5 fewer - 28 more)			

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care Hydroxychloroquine		Certainty of the evidence (Quality of evidence)	Plain text summary
Mechanical ventilation	Odds ratio 1.2 (CI 95% 0.83 - 1.81) Based on data from 6,379 patients in 5 studies. (Randomized controlled)	105 per 1000	123 per 1000	Moderate Due to borderline risk of bias and serious imprecision ³	Hydroxychloroquine probably does not reduce mechanical ventilation.
Viral clearance 7 days	Odds ratio 1.08 (CI 95% 0.25 - 4.78) Based on data from 280 patients in 4 studies. (Randomized controlled)	483 per 1000	502 per 1000	Very Low Due to very serious imprecision ⁴	The effect of hydroxychloroquine on viral clearance is very uncertain.
Admission to hospital	Odds ratio 0.39 (CI 95% 0.12 - 1.28) Based on data from 465 patients in 1 studies. (Randomized controlled)	47 per 1000	19 per 1000	Very Low Due to very serious imprecision and serious indirectness ⁵	The effect of hydroxychloroquine on admission to hospital is uncertain.
Cardiac toxicity	Based on data from 3,287 patients in 7 studies. (Randomized controlled)	46 per 1000	56 per 1000	Very Low Due to serious imprecision, risk of bias, and indirectness ⁶	The effect of hydroxychloroquine on cardiac toxicity is uncertain.
Diarrhoea	Odds ratio 1.95 (CI 95% 1.4 - 2.73) Based on data from 979 patients in 6 studies. (Randomized controlled)	149 per 1000	255 per 1000	Low Due to serious imprecision and risk of bias ⁷	Hydroxychloroquine may increase the risk of diarrhoea.
Nausea/ vomiting	Odds ratio 1.74 (CI 95% 1.26 - 2.41) Based on data from 1,429 patients in 7 studies. (Randomized controlled)	99 per 1000	161 per 1000	Low Due to serious imprecision and risk of bias ⁸	Hydroxychloroquine may increase the risk of nausea and vomiting.
Delirium	Odds ratio 1.59 (CI 95% 0.77 - 3.28) Based on data from 423 patients in 1 studies. (Randomized controlled)	62 per 1000	95 per 1000	Very Low Due to very serious imprecision and serious indirectness ⁹	The effect of hydroxychloroquine on delirium is uncertain.

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care Hydroxychloroquine		Certainty of the evidence (Quality of evidence)	Plain text summary
Time to clinical improvement	Lower better Based on data from: 479 patients in 5 studies. (Randomized controlled)	11 days (Mean)	9 days (Mean)	Very Low Due to serious risk of bias, imprecision, and indirectness ¹⁰	The effect of hydroxychloroquine on time to clinical improvement is uncertain.
Duration of hospitalization	Lower better Based on data from: 5,534 patients in 5 studies. (Randomized controlled)	12.8 days (Mean)	12.9 days (Mean)	Low Due to serious imprecision and serious risk of bias ¹¹	Hydroxychloroquine may have no effect on duration of hospitalization.
Time to viral clearance	Lower better Based on data from: 440 patients in 5 studies. (Randomized controlled)	9.7 days (Mean)	10.6 days (Mean)	Very Low Due to serious risk of bias and very serious imprecision ¹²	The effect of hydroxychloroquine on time to viral clearance is uncertain.
Adverse events leading to drug discontinuation	Based on data from: 210 patients in 3 studies. (Randomized controlled)	Two of 108 patients randomized to hydroxychloroquine discontinued treatment because of adverse effects. None of 102 patients did so in the placebo/standard care group.		Very Low Due to extremely serious imprecision ¹³	The effect of hydroxychloroquine on adverse events leading to drug discontinuation is uncertain.

1. Systematic review (3). **Baseline/comparator:** Control arm of reference used for intervention. We elected to use the control arm of the WHO solidarity trial, reflecting usual care across countries participating in the trial.
2. **Risk of bias: Serious.** We rated two trials as high risk of bias due to high or probably high risk of bias in deviations from the intended intervention. . **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** The 95% CI crosses the minimally important difference (2% reduction in mortality). . **Publication bias: No serious.**
3. **Risk of bias: Serious. Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**
4. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Wide confidence intervals. **Publication bias: No serious.**
5. **Inconsistency: No serious. Indirectness: Serious. Imprecision: Very Serious. Publication bias: No serious.**
6. **Risk of bias: Serious.** unblinded studies -> cardiac toxicity differential detection. **Inconsistency: No serious. Indirectness: Serious.** Studies measured serious cardiac toxicity differently.. **Imprecision: Serious.**
7. **Risk of bias: Serious.** Concerns mitigated because of large effect and indirect evidence showing consistent results. **Imprecision: Serious.** OIS not met. **Upgrade: Large magnitude of effect.**
8. **Risk of bias: Serious.** Concerns mitigated because of large effect and indirect evidence showing consistent results. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** OIS not met.. **Publication bias: No serious. Upgrade: Large magnitude of effect.**
9. **Indirectness: Serious.** This outcome was not collected systematically and the definition of delirium was not specified.. **Imprecision: Very Serious.**
10. **Risk of bias: Serious. Inconsistency: No serious. Indirectness: Serious.** Studies measured clinical improvement

differently.. Imprecision: Serious. Publication bias: No serious.

11. Risk of bias: Serious. Indirectness: No serious. Imprecision: Serious. Wide confidence intervals.

12. Risk of bias: Serious. Imprecision: Very Serious.

13. Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious. Publication bias: No serious.

7.3 Lopinavir/ritonavir (published December 17 2020)

The third version of the WHO living guideline addressed the use of lopinavir/ritonavir (and hydroxychloroquine, see above) in patients with COVID-19. It followed the pre-print publication of the WHO SOLIDARITY Trial on 15 October 2020, reporting results on treatment with remdesivir, hydroxychloroquine and lopinavir-ritonavir in hospitalized patients with COVID-19 (50). The role of these drugs in clinical practice has remained uncertain, with limited prior trial evidence. The WHO SOLIDARITY Trial adds 11,266 randomized patients (2570 to remdesivir, 954 to hydroxychloroquine, and 1411 to lopinavir-ritonavir, 6,331 to usual care) and had the potential to change practice (13, 50).

The evidence

For lopinavir/ritonavir, the evidence summary was based on 7 trials with 7429 participants. Of note, none of the included studies enrolled children or adolescents under the age of 19 years old (Table 4).

Table 4. Summary of trials and trial characteristics informing the lopinavir/ritonavir recommendation (trials = 7, total patients = 7429)

Geographic region	Region of the Americas South-East Asia Region Western Pacific Region European Region Eastern Mediterranean Region	Region of the Americas (0 trials, 0 patients) South-East Asia and Western Pacific Regions (5 trials, 535 patients) European Region (2 trials, 6894 patients) Middle East (0 trials, 0 patients)
Severity of illness ^a	Non-severe Severe Critically ill	Mild/Moderate (4 trials, 336 patients) Severe (1 trials, 199 patients) Critically ill (0 trials, 0 patients)
Mechanically ventilated at baseline ^b	Mean (range), %	7.3 (0–16.1)
Age ^c	Mean (range of means), years	52.6 (42.5–66.2)
Sex	Mean (range of means), % women	48.7 (38.9–61.7)
Loading doses Day 1 ^d	Mean (range of means), mg	
Total cumulative doses (lopinavir/ ritonavir) ^e	Median (range), mg	11200/2800(8000–11 200/2000–2800)
Duration of therapy ^f	Median (range), days	14 (10–14)
Type of care	n (%) inpatient n (%) outpatient	Inpatient: 7429 (100) Outpatient: 0 (0)
Trial participants	Median (range)	101 (60–5040)
Concomitant use of corticosteroids ^g	Mean (range across trials that report this), %	17.1 (0–32.3)

Notes:

^a 2 trials did not report the disease severity of patients.

^b 3 trials did not report proportion of mechanical ventilation at baseline.

^c 2 trials did not report the age of patients.

^d No trial reported loading dose.

^e 1 trial did not report cumulative doses; 2 trials only reported range of treatment duration.

^f 1 trial did not report the duration of therapy, 2 trials used a range of treatment duration.

^g 2 trials did not report the concomitant use of corticosteroids.

Baseline risk

The absolute effects of treatment are informed by the prognosis (i.e. baseline risk estimates) combined with the relative estimates of effects (e.g. risk ratio, odds ratio) obtained from the NMA.

The control arm of the WHO SOLIDARITY Trial (13), performed across a wide variety of countries and geographical regions, was identified by the GDG panel as representing the most relevant source of evidence to make the baseline risk estimates for the outcomes of mortality and mechanical ventilation. The rationale for selecting the WHO SOLIDARITY Trial was to reflect the overall prognosis of the global population for which the WHO guideline recommendations are made. When applying the evidence to a particular patient or setting, the individual or setting's risk of mortality and mechanical ventilation should be considered. In view of the study designs, the GDG determined that for other outcomes using the median or mean of all patients randomized to usual care across the included studies would provide the most reliable estimate of baseline risk.

Subgroup analysis

For lopinavir/ritonavir, the GDG panel requested subgroup analyses based on age (considering children vs younger adults [e.g. under 70 years] vs older adults [e.g. 70 years or older]), and illness severity (non-severe vs severe vs critical COVID). The GDG discussed other potential subgroups of interest including time from onset of symptoms until initiation of therapy and concomitant medications, but recognized that these analyses would not be possible without access to individual participant data and/or more detailed reporting from the individual trials.

Info Box

The recommendation concerning lopinavir-ritonavir was published December 17 2020 as the [third version](#) of the WHO living guideline and in the BMJ as [Rapid Recommendations](#). No changes were made for the lopinavir/ritonavir recommendation in this fourth version of the guideline. Please view the section text for a summary of the evidence requested to inform the recommendation, triggered by the WHO Solidarity trial.

Recommendation against

We recommend against administering lopinavir/ritonavir for treatment of COVID-19.

Remark: This recommendation applies to patients with any disease severity and any duration of symptoms.

Evidence to decision

Benefits and harms

The GDG panel found a lack of evidence that lopinavir/ritonavir improved outcomes that matter to patients such as reduced mortality, need for mechanical ventilation, time to clinical improvement and others. For mortality and need for mechanical ventilation this was based on moderate certainty evidence, for the other outcomes low or very low certainty evidence.

There was low certainty evidence that lopinavir/ritonavir may increase the risk of diarrhoea and nausea and vomiting, a finding consistent with the indirect evidence evaluating its use in patients with HIV. Diarrhoea and vomiting may increase the risk of hypovolaemia, hypotension and acute kidney injury, especially in settings where health care resources are limited. There was an uncertain effect on viral clearance and acute kidney injury.

Subgroup analysis indicated no effect modification based on severity of illness (comparing either critical vs severe/non-severe or non-severe vs critical/severe) or age (comparing those aged < 70 years versus those 70 years and older). As there was no evidence of a statistical subgroup effect, we did not formally evaluate using the ICEMAN tool.

Certainty of the evidence

The evidence is based on a linked systematic review and NMA of seven randomized controlled trials; pooling data from 7429 patients hospitalized with various severities of COVID-19 and variably reporting the outcomes of interest to the guideline panel (3). The panel agreed that there was moderate certainty for mortality and need for mechanical ventilation, low certainty for diarrhoea, nausea and duration of hospitalization and very low certainty in the estimates of effect for viral clearance, acute kidney injury and time to clinical improvement. Most outcomes were lowered for risk of bias and imprecision (wide confidence intervals which do not exclude important benefit or harm).

Preference and values

Applying the agreed values and preferences (see Evidence section above), the GDG inferred that almost all well-informed patients would not want to receive lopinavir/ritonavir given the evidence suggested there was probably no effect on mortality or need for mechanical ventilation and there was a risk of adverse events including diarrhoea and nausea and vomiting. The panel did not expect there would be much variation in values and preferences between patients when it came to this intervention.

Resources and other considerations

Although the cost of lopinavir/ritonavir is not as high as some other investigational drugs for COVID-19, and the drug is generally available in most health care settings, the GDG raised concerns about opportunity costs and the importance of not drawing attention and resources away from best supportive care or the use of corticosteroids in severe COVID-19.

Justification

When moving from evidence to the strong recommendation against the use of lopinavir/ritonavir for patients with COVID-19, the panel emphasized the moderate certainty evidence of probably no reduction in mortality or need for mechanical ventilation. It also noted the evidence suggesting possible harm associated with treatment, with increased nausea and diarrhoea. The GDG did not anticipate important variability in patient values and preferences, and other contextual factors, such as resource considerations, accessibility, feasibility and impact on health equity would not alter the recommendation (see summary of these factors under Evidence to decision).

Subgroup analysis

The panel did not find any evidence of a subgroup effect across patients with different levels of disease severity, or between adults and older adults and therefore did not make any subgroup recommendation for this drug. Although the trials did not report subgroup effects by time from symptom onset, many of the trials enrolled patients with patients early in the disease course. The strong recommendation is applicable across disease severity and age groups.

Applicability

None of the included RCTs enrolled children, and therefore the applicability of this recommendation to children is currently uncertain. However, the panel had no reason to think that children with COVID-19 would respond any differently to treatment with lopinavir/ritonavir. There were similar considerations in regards to pregnant women, with no data directly examining this population, but no rationale to suggest they would respond differently than other adults. In patients using lopinavir/ritonavir for HIV infection, it should generally be continued while receiving care for COVID-19.

Uncertainties

Please see end of document for residual uncertainties (Section 8). The GDG panel felt that it was unlikely future studies would identify a subgroup of patients that are likely to benefit from lopinavir/ritonavir.

Additional considerations

In patients who have undiagnosed or untreated HIV, use of lopinavir/ritonavir alone may promote HIV resistance to important antiretrovirals. Widespread use of lopinavir/ritonavir for COVID-19 may cause drug shortages for people living with HIV.

Clinical question/ PICO

Population: Patients with COVID-19 (all disease severities)
Intervention: Lopinavir-ritonavir
Comparator: Standard care

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Plain text summary
		Standard care	Lopinavir- ritonavir		
Mortality	Odds ratio 1 (CI 95% 0.82 - 1.2) Based on data from 8,061 patients in 4 studies. ¹ (Randomized controlled)	106 per 1000	106 per 1000	Moderate Due to borderline risk of bias and imprecision ²	Lopinavir-ritonavir probably has no effect on mortality
Mechanical ventilation	Relative risk 1.16 (CI 95% 0.98 - 1.36) Based on data from 7,579 patients in 3 studies. ³ (Randomized controlled)	105 per 1000	122 per 1000	Moderate Due to borderline risk of bias and imprecision ⁴	Lopinavir-ritonavir probably does not reduce mechanical ventilation
Viral clearance	Odds ratio 0.35 (CI 95% 0.04 - 1.97) Based on data from 171 patients in 2 studies. (Randomized controlled)	483 per 1000	246 per 1000	Low Due to serious risk of bias, Due to very serious imprecision ⁵	the effects of lopinavir- ritonavir on viral clearance is very uncertain
Acute kidney injury	Relative risk Based on data from 259 patients in 2 studies. (Randomized controlled)	45 per 1000	25 per 1000	Very Low Due to serious risk of bias and very serious imprecision, Due to very serious imprecision ⁶	The effect of lopinavir- ritonavir on acute kidney injury is uncertain
Diarrhoea	Odds ratio 4.28 (CI 95% 1.99 - 9.18) Based on data from 370 patients in 4 studies. (Randomized controlled)	67 per 1000	235 per 1000	Moderate Due to serious risk of bias and imprecision, Upgraded due to Large magnitude of effect ⁷	Lopinavir-ritonavir may increase the risk of diarrhoea.
Nausea/ vomiting	Relative risk Based on data from 370 patients in 4 studies. ⁸ (Randomized controlled)	17 per 1000	177 per 1000	Moderate Due to serious risk of bias and imprecision ⁹	Lopinavir-ritonavir may increase the risk of nausea/vomiting

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Plain text summary
		Standard care	Lopinavir- ritonavir		
		(CI 95% 100 more - 210 more)			
Time to clinical improvement	Lower better Based on data from: 199 patients in 1 studies. (Randomized controlled)	11 days (Mean)	10 days (Mean)	Very Low Due to serious risk of bias, Due to very serious imprecision ¹⁰	The effect of lopinavir- ritonavir improves on time to clinical improvement is very uncertain
Duration of hospitalization	Lower better Based on data from: 5,239 patients in 2 studies. (Randomized controlled)	12.8 days (Mean)	12.5 days (Mean)	Low Due to serious risk of bias and imprecision ¹¹	Lopinavir-ritonavir may have no effect on duration of hospitalization

1. Systematic review. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** (3),
2. **Risk of bias: No serious.** We rated two trials as high risk of bias due to high or probably high risk of bias in deviations from the intended intervention.. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** The 95% CI crosses the minimally important difference (2% reduction in mortality).. **Publication bias: No serious.**
3. Systematic review. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** (3),
4. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**
5. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Wide confidence intervals. **Publication bias: No serious.**
6. **Risk of bias: Serious. Inconsistency: No serious. Imprecision: Very Serious.** Wide confidence intervals. **Publication bias: No serious.**
7. **Risk of bias: Serious.** Concerns mitigated because of large effect and indirect evidence showing consistent results. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Few patients and events. **Publication bias: No serious. Upgrade: Large magnitude of effect.**
8. Systematic review. **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** (3),
9. **Risk of bias: Serious.** Concerns mitigated because of large effect and indirect evidence showing consistent results. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Few patients and events. **Publication bias: No serious. Upgrade: Large magnitude of effect.**
10. **Risk of bias: Serious. Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Wide confidence intervals, low number of patients. **Publication bias: No serious.**
11. **Risk of bias: Serious. Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence intervals. **Publication bias: No serious.**

7.4 Remdesivir (published Nov 20 2020)

The second version of the WHO living guideline addressed the use of remdesivir in patients with COVID-19. It followed the pre-print publication of the WHO SOLIDARITY trial on 15 October, 2020, reporting results on treatment with remdesivir, hydroxychloroquine and lopinavir-ritonavir in hospitalized patients with COVID-19 (13). The role of these drugs in clinical practice has remained uncertain, with limited prior trial evidence. The WHO SOLIDARITY trial adds 11,266 randomized patients (2570 to remdesivir, 954 to hydroxychloroquine, and 1411 to lopinavir-ritonavir, 6,331 to usual care) and had the potential to change

practice (13).

The WHO GDG started with developing trustworthy recommendations on remdesivir, followed by the now published recommendations on hydroxychloroquine and lopinavir-ritonavir in the third update. Remdesivir is a novel monophosphoramidate adenosine analogue prodrug which is metabolized to an active tri-phosphate form that inhibits viral RNA synthesis. Remdesivir has in vitro and in vivo antiviral activity against several viruses, including SARS-CoV2. Remdesivir is widely used in many countries, with several guidelines recommending its use in patients with severe or critical COVID-19 (51, 52).

The evidence

The GDG panel requested an update of the living NMA of RCTs of drug treatments for COVID-19, based around important clinical questions to be addressed in the recommendations. The rating of importance of outcomes, selection of estimates for baseline risk and considerations about values and preferences were similar to what is presented in Section 5.

Based on 4 trials with 7333 participants (13, 53-55), the NMA provided relative estimates of effect for patient-important outcomes (Table 4). Of note, none of the included studies enrolled children or adolescents under the age of 19 years old.

Table 5. Summary of trials and trial characteristics informing the remdesivir recommendation

Study	N	Country	Mean age (years)	Severity (as per WHO criteria)	% IMV (at baseline)	Treatments (dose and duration)	Outcomes
Biegel (ACTT-1)	1063	United States, Europe, Asia	58.9	Non-severe (11.3%) Severe ^a (88.7%)	44.1%	Remdesivir IV (100 mg/day for 10 days)	-Mortality -Adverse events -Time to clinical improvement
Spinner (SIMPLE MODERATE)*	596	United States, Europe, Asia	56-58	Non-severe (100%)	0%	Remdesivir IV (200 mg at day 1, then 100 mg for 4 days or 9 days)	-Mortality -Time to clinical improvement -Duration of hospitalization -Mechanical ventilation -Adverse events
Pan (SOLIDARITY)	5451	Worldwide	< 50 35% 50-70 47% > 70 18%	Non-severe (24%) Severe ^b (67%) Critical (9%)	8.9%	Remdesivir IV (200 mg at day 1, then 100 mg day 2-10)	-Mortality -Mechanical ventilation
Wang	237	China	65	Severe ^c (100%)	16.1%	Remdesivir IV (100 mg/day for 10 days)	-Mortality -Mechanical ventilation -Adverse events -Viral clearance -Duration of hospitalization -Duration of ventilation -Time to clinical improvement

IMV: invasive mechanical ventilation; IV: intravenous; N: number; NR: not reported; Sx: symptom.

Severity criteria based on WHO definitions unless otherwise stated. a – defined severe as SpO₂ < 94% on room air OR respiratory rate > 24 breaths per minute; b – defined severe as requiring oxygen support; c – defined severe as SpO₂ < 94% on room air. Notes:

*Only SIMPLE MODERATE was included in the analysis, as SIMPLE SEVERE did not have a placebo/usual care arm.

Subgroup analysis

The GDG panel requested subgroup analyses based on age (considering children vs adults vs older people), illness severity (non-severe vs severe vs critical COVID – see subgroup under Section 7 - Recommendations for therapeutics section for details), and duration of remdesivir therapy (5 days vs longer than 5 days). The GDG discussed other potential subgroups of interest including time from onset of symptoms until initiation of therapy, concomitant medications (especially corticosteroids) however recognized these analyses would not be possible without access to individual participant data. To this last point, the panel recognized that usual care is likely variable between centres, regions and evolved over time. However, given all of the data comes from RCTs, use of these co-interventions that comprise usual care should be balanced between study patients randomized to either the intervention or usual care arms.

Following the panel's request, the NMA team performed subgroup analyses in order to assess for effect modification which, if present, could mandate distinct recommendations by subgroups. From the data available from the included trials, subgroup analysis was only possible for severity of illness and the outcome of mortality. This subgroup analysis was performed using a random effects frequentist analysis based on the three WHO severity definitions. A post-hoc Bayesian analysis was also performed, which incorporated meta-regression using study as a random effect. This latter approach has the advantage of more accurately accounting for within-study differences but can only compare two subgroups at a time. The panel used a pre-specified framework incorporating the ICEMAN tool to assess the credibility of subgroup findings (13).

Info Box

The recommendation concerning remdesivir was published November 20 2020 as the [second version of the WHO living guideline](#) and in the BMJ as [Rapid Recommendations](#). No changes were made for the remdesivir recommendation in this third version of the guideline. Please view the section text for a summary of the evidence requested to inform the recommendation, triggered by the WHO SOLIDARITY trial.

Hospitalized patients with COVID-19 infection, regardless of disease severity

Conditional recommendation against

We suggest against administering remdesivir in addition to usual care

Practical info

The GDG made a conditional recommendation against using remdesivir for treatment of hospitalized patients with COVID-19. If administration of remdesivir is considered, it should be noted that its use is contraindicated in those with liver (ALT >5 times normal at baseline) or renal (eGFR <30 mL/minute) dysfunction. To date, it can only be administered intravenously, and it has relatively limited availability.

Evidence to decision

Benefits and harms

The GDG panel found a lack of evidence that remdesivir improved outcomes that matter to patients such as reduced mortality, need for mechanical ventilation, time to clinical improvement and others. However, the low certainty evidence for these outcomes, especially mortality, does not prove that remdesivir is ineffective; rather, there is insufficient evidence to confirm that it does improve patient-important outcomes.

There was no evidence of increased risk of severe adverse events (SAEs) from the trials.. However, further pharmacovigilance is needed because SAEs are commonly underreported and rare events could be missed, even in large RCTs.

A subgroup analysis indicated that remdesivir treatment possibly increased mortality in the critically ill and possibly reduced mortality in the non-severely and severely ill. The panel judged the overall credibility of this subgroup effect (evaluated using the ICEMAN tool) to be insufficient to make subgroup recommendations. The overall low certainty evidence on the benefits and harms of remdesivir, driven by risk of bias and imprecision limitations in the included studies, also contributed to the judgement.

Certainty of the evidence

Low

The evidence is based on a linked systematic review and NMA of four RCTs; pooling data from 7333 patients hospitalized with various severities of COVID-19 and variably reporting the outcomes of interest to the guideline panel (3). The panel agreed that there was low certainty in the estimates of effect for all patient-important outcomes across benefits and harms, mostly driven by risk of bias and imprecision (wide confidence intervals which do not exclude important benefit or harm). There was very low certainty evidence for viral clearance and delirium.

Preference and values

Substantial variability is expected or uncertain

Applying the agreed values and preferences (see Evidence section above), the GDG inferred that most patients would be reluctant to use remdesivir given the evidence left high uncertainty regarding effects on mortality and the other prioritized outcomes. This was particularly so as any beneficial effects of remdesivir, if they do exist, are likely to be small and the possibility of important harm remains. The panel acknowledged, however, that values and preferences are likely to vary, and there will be patients and clinicians who choose to use remdesivir given the evidence has not excluded the possibility of benefit.

Resources and other considerations

Important issues, or potential issues not investigated

A novel therapy typically requires higher certainty evidence of important benefits than currently available for remdesivir, preferably supported wherever possible by cost-effectiveness analysis. In the absence of this information, the GDG raised concerns about opportunity costs and the importance of not drawing attention and resources away from best supportive care or the use of corticosteroids in severe COVID-19. It was noted that remdesivir is administered only by the intravenous route currently, and that global availability is currently limited.

Justification

When moving from evidence to the conditional recommendation against the use of remdesivir for patients with COVID-19, the panel emphasized the evidence of possibly no effect on mortality, need for mechanical ventilation, recovery from symptoms and other patient-important outcomes, albeit of low certainty; it also noted the anticipated variability in patient values and preferences, and other contextual factors, such as resource considerations, accessibility, feasibility and impact on health equity (see summary of these factors under Evidence to decision).

Importantly, given the low certainty evidence for these outcomes, the panel concluded that the evidence did not prove that remdesivir has no benefit; rather, there is no evidence based on currently available data that it does improve patient-important outcomes. Especially given the costs and resource implications associated with remdesivir, but consistent with the approach that should be taken with any new drug, the panel felt the responsibility should be on demonstrating evidence of efficacy, which is not established by the currently available data. The panel noted that there was no evidence of increased risk of SAEs in patients receiving remdesivir, at least from the included trials. Further pharmacovigilance is required to confirm this, as SAEs are commonly underreported and rare events would be missed, even in large RCTs.

Subgroup analysis

The panel carefully considered a potential subgroup effect across patients with different levels of disease severity, suggesting a possible increase in mortality in the critically ill and a possible reduction in mortality in the non-severely and severely ill. For this analysis, critical illness was defined as those requiring invasive or non-invasive ventilation, severe illness as those requiring oxygen therapy (but not meeting critical illness criteria), and non-severe as all others. Patients requiring high-flow nasal cannula represented a small proportion and were characterized as either severe (SOLIDARITY) (13) or critical (ACTT-1) (55). The analysis focused on within-study subgroup comparisons across the different severities, and therefore the SIMPLE-MODERATE trial could not be included in the subgroup analysis as it only enrolled patients with non-severe COVID-19. The panel reviewed the results of both the random effects frequentist analysis and the post-hoc Bayesian analysis which incorporated meta-regression using study as a random effect.

The GDG panel judged the credibility in the subgroup analysis assessing differences in mortality by severity of illness to be

insufficient to make subgroup recommendations. Important factors influencing this decision included a lack of a priori hypothesized direction of subgroup effect by trial investigators, little or no previously existing supportive evidence for the subgroup finding, and relatively arbitrary cut points used to examine the subgroups of interest. The overall low certainty evidence for the benefits and harms of remdesivir, driven by risk of bias and imprecision limitations, also contributed to the judgement. The panel highlighted that despite the conditional recommendation against remdesivir, they support further enrolment into RCTs evaluating remdesivir, especially to provide higher certainty of evidence for specific subgroups of patients.

The panel had *a priori* requested analyses of other important subgroups of patients including children and older persons, but there were no data to address these groups specifically. None of the included RCTs enrolled children, and although older people were included in the trials, their outcomes were not reported separately. Also, there is no pharmacokinetic or safety data on remdesivir for children. Given this, the applicability of this recommendation to children is currently uncertain.

Clinical question/ PICO

Population: Patients with COVID-19 infection (all disease severities)
Intervention: Remdesivir + usual care
Comparator: Usual care

Summary

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Plain text summary
		Standard care	Remdesivir		
Mortality 28 days	Odds ratio 0.9 (CI 95% 0.7 - 1.12) Based on data from 7,333 patients in 4 studies. ¹ (Randomized controlled)	106 per 1000	96 per 1000	Low Due to serious risk of bias and serious imprecision ²	Remdesivir possibly has little or no effect on mortality.
Mechanical ventilation	Odds ratio 0.89 (CI 95% 0.76 - 1.03) Based on data from 6,549 patients in 4 studies. ³ (Randomized controlled)	105 per 1000	95 per 1000	Low Due to serious risk of bias and serious imprecision ⁴	Remdesivir possibly has little or no effect on mechanical ventilation.
Serious adverse events leading to discontinuation	Odds ratio 1 (CI 95% 0.37 - 3.83) Based on data from 1,894 patients in 3 studies. ⁵ (Randomized controlled)	15 per 1000	15 per 1000	Low Due to very serious imprecision ⁶	Remdesivir possibly has little or no effect on serious adverse events leading to discontinuation.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Plain text summary
		Standard care	Remdesivir		
Viral clearance 7 days	Odds ratio 1.06 (CI 95% 0.06 - 17.56) Based on data from 196 patients in 1 studies. ⁷ (Randomized controlled)	483 per 1000	498 per 1000	Very Low Due to very serious imprecision ⁸	The effect of remdesivir on viral clearance is uncertain.
Acute kidney injury	Odds ratio 0.85 (CI 95% 0.51 - 1.41) Based on data from 1,281 patients in 2 studies. ⁹ (Randomized controlled)	56 per 1000	48 per 1000	Low Due to serious imprecision and serious indirectness ¹⁰	Remdesivir possibly has little or no effect on acute kidney injury.
Delirium	Odds ratio 1.22 (CI 95% 0.48 - 3.11) Based on data from 1,048 patients in 1 studies. ¹¹ (Randomized controlled)	16 per 1000	19 per 1000	Very Low Due to very serious imprecision and serious indirectness ¹²	We are uncertain whether remdesivir increases or decreases delirium
Time to clinical improvement	Measured by: days Lower better Based on data from: 1,882 patients in 3 studies. ¹³ (Randomized controlled)	11 days	9 days	Low Due to serious imprecision and serious indirectness ¹⁴	Remdesivir possibly has little or no effect on time to clinical improvement.
Duration of hospitalization	Measured by: days Lower better Based on data from: 1,882 patients in 3 studies. ¹⁵ (Randomized controlled)	12.8 days	12.3 days	Low Due to serious imprecision and serious indirectness ¹⁶	Remdesivir possibly has little or no effect on duration of hospitalization.
Duration of ventilation	Measured by: days Lower better Based on data from: 440 patients in 2 studies. ¹⁷ (Randomized controlled)	14.7 days	13.4 days	Low Due to very serious imprecision ¹⁸	Remdesivir possibly has little or no effect on duration of ventilation.

1. Systematic review (3). **Baseline/comparator:** Control arm of reference used for intervention (50).
2. **Risk of bias: Serious.** We rated two trials as high risk of bias due to high or probably high risk of bias in deviations from the intended intervention. . **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** The 95% CI crosses the minimally important difference (2% reduction in mortality). . **Publication bias: No serious.**
3. Systematic review (3) . **Baseline/comparator:** Control arm of reference used for intervention (50).
4. **Risk of bias: Serious. Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** Wide confidence

intervals. **Publication bias: No serious.**

5. Systematic review (3). **Baseline/comparator:** Systematic review (3). Used the median or mean of all patients randomized to usual care across the included studies..

6. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Wide confidence intervals. **Publication bias: No serious.**

7. Systematic review (3). **Baseline/comparator:** Systematic review (3). Used the median or mean of all patients randomized to usual care across the included studies..

8. **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very Serious.** Wide confidence intervals. **Publication bias: No serious.**

9. Systematic review (3). **Baseline/comparator:** Systematic review (3). Used the median or mean of all patients randomized to usual care across the included studies..

10. **Inconsistency: No serious. Indirectness: Serious.** Studies used change in serum creatinine rather than patient-important measures of acute kidney injury.. **Imprecision: Serious.** Wide 95% credible intervals.. **Publication bias: No serious.**

11. Systematic review (3). **Baseline/comparator:** Systematic review (3). Used the median or mean of all patients randomized to usual care across the included studies..

12. **Indirectness: Serious.** Differences between the outcomes of interest and those reported (e.g short-term/surrogate,not patient-important). **Imprecision: Very Serious.**

13. Systematic review (3). Used the median or mean of all patients randomized to usual care across the included studies.. **Baseline/comparator:** Control arm of reference used for intervention.

14. **Inconsistency: No serious. Indirectness: Serious. Imprecision: Serious. Publication bias: No serious.**

15. Systematic review (3). Used the median or mean of all patients randomized to usual care across the included studies.. **Baseline/comparator:** Control arm of reference used for intervention.

16. **Indirectness: Serious. Imprecision: Serious.** Wide confidence intervals.

17. Systematic review (3). Used the median or mean of all patients randomized to usual care across the included studies.. **Baseline/comparator:** Control arm of reference used for intervention.

18. **Imprecision: Very Serious.** Wide confidence intervals.

7.5 Systemic corticosteroids (published 2 September 2020)

This guideline was triggered on 22 June 2020 by the publication of the preliminary report of the RECOVERY trial, which has now been published as a peer-reviewed paper (12). Corticosteroids are listed in the WHO Model List of Essential Medicines, readily available globally at a low cost, and of considerable interest to all stakeholder groups. The guideline panel was informed by combining two meta-analyses which pooled data from eight randomized trials (7184 participants) of systemic corticosteroids for COVID-19 (3, 58). The panel discussions were also informed by two other meta-analyses, which were already published and pooled data about the safety of systemic corticosteroids in distinct but relevant patient populations.

On 17 July 2020, the panel reviewed evidence from eight RCTs (7184 patients) evaluating systemic corticosteroids versus usual care in COVID-19. RECOVERY, the largest of the seven trials, from which mortality data were available by subgroup (severe and non-severe), evaluated the effects of dexamethasone 6 mg given once daily (oral or intravenous) for up to 10 days in 6425 hospitalized patients in the United Kingdom (2104 were randomized to dexamethasone and 4321 were randomized to usual care) (12). At the time of randomization, 16% were receiving invasive mechanical ventilation or extracorporeal membrane oxygenation; 60% were receiving oxygen only (with or without non-invasive ventilation); and 24% were receiving neither.

The data from seven other smaller trials included 63 non-critically ill patients and approximately 700 critically ill patients (definitions of critical illness varied across studies). For the latter, patients were enrolled up to 9 June 2020, and approximately four-fifths were invasively mechanically ventilated; approximately half were randomized to receive corticosteroid therapy, and half randomized to no corticosteroid therapy. Corticosteroid regimens included: methylprednisolone 40 mg every 12 hours for 3 days and then 20 mg every 12 hours for 3 days (GLUCOCOVID) (68); dexamethasone 20 mg daily for 5 days followed by 10 mg daily for 5 days (two trials, DEXA-COVID19, CoDEX) (60, 64); hydrocortisone 200 mg daily for 4 to 7 days followed by 100 mg daily for 2 to 4 days and then 50 mg daily for 2 to 3 days (one trial, CAPE-COVID) (59); hydrocortisone 200 mg daily for 7 days (one trial, REMAP-CAP) (63);

methylprednisolone 40 mg every 12 hours for 5 days (one trial, Steroids-SARI) (61).

Seven of the trials were conducted in individual countries (Brazil, China, Denmark, France, Spain) whilst REMAP-CAP was an international study (recruiting in 14 European countries, Australia, Canada, New Zealand, Saudi Arabia and the United Kingdom). All trials reported mortality 28 days after randomization, except for one trial at 21 days and another at 30 days. Because the mortality data from one trial (GLUCOCOVID, n=63) were not reported by subgroup, the panel reviewed only the data pertaining to the outcome of mechanical ventilation from this trial (68). An additional trial, which randomized hospitalized patients with suspected SARS-CoV-2 infection, published on 12 August 2020 (MetCOVID) (62), was included as a supplement in the prospective meta-analysis (PMA) publication, as it was registered after the searches of trial registries were performed. The supplement showed that inclusion would not change results other than reduce inconsistency.

Subgroup effect for mortality

While all other trials evaluated systemic corticosteroids exclusively in critically ill patients, the RECOVERY Trial enrolled hospitalized patients with COVID-19. The panel considered the results of a subgroup analysis of the RECOVERY Trial suggesting that the relative effects of systemic corticosteroids varied as a function of the level of respiratory support received at randomization. On the basis of the peer-reviewed criteria for credible subgroup effects (42), the panel determined that the subgroup effect was sufficiently credible to warrant separate recommendations for severe and non-severe COVID-19.

However, acknowledging that during a pandemic, access to health care may vary considerably over time as well as between different countries, the panel decided against defining patient populations concerned by the recommendations on the basis of access to health interventions (i.e. hospitalization and respiratory support). Thus, the panel attributed the effect modification in the RECOVERY Trial to illness severity.

The panel also acknowledged the existence of variable definitions for severity and use of respiratory support interventions. The WHO clinical guidance for COVID-19 published on 27 May 2020 (version 3) defined severity of COVID-19 by clinical indicators, but modified the oxygen saturation threshold from 94% to 90% (16), in order to align with previous WHO guidance (17). See Section 6 for the WHO severity criteria and Infographic below for three disease severity groups for which the recommendations apply in practice.

Info Box

The recommendations for corticosteroids below were first published as [WHO living guidelines](#) 2 September 2020, and as [BMJ Rapid Recommendations](#) 5 September 2020, including links to MAGICapp. Please visit the [WHO website](#) guidelines for details (e.g. composition of the guideline panel) and view section text to understand what evidence the panel applied in creating these recommendations. By 15 November 2020 there was no new evidence to suggest any change in the recommendations, as identified in the living systematic review and NMA informing this living guideline.

For patients with severe or critical COVID-19-infection (see disease severity criteria above)

Recommended

We recommend systemic corticosteroids rather than no corticosteroids

Practical info

Route—Systemic corticosteroids may be administered both orally and intravenously. Of note, while the bioavailability of dexamethasone is very high (that is, similar concentrations are achieved in plasma after oral and intravenous intake), critically ill patients may be unable to absorb any nutrients or medications due to intestinal dysfunction. Clinicians therefore may consider administering systemic corticosteroids intravenously rather than orally if intestinal dysfunction is suspected.

Duration—While more patients received corticosteroids in the form of dexamethasone 6 mg daily for up to 10 days, the total

duration of regimens evaluated in the seven trials varied between five and 14 days, and treatment was generally discontinued at hospital discharge (that is, the duration of treatment could be less than the duration stipulated in the protocols).

Dose—The once daily dexamethasone formulation may increase adherence. A dose of 6 mg of dexamethasone is equivalent (in terms of glucocorticoid effect) to 150 mg of hydrocortisone (that is, 50 mg every 8 hours), 40 mg of prednisone, or 32 mg of methylprednisolone (8 mg every 6 hours or 16 mg every 12 hours).

Monitoring—It would be prudent to monitor glucose levels in patients with severe and critical covid-19, regardless of whether the patient is known to have diabetes.

Timing—The timing of therapy from onset of symptoms was discussed by the panel. The RECOVERY investigators reported a subgroup analysis suggesting that the initiation of therapy seven days or more after symptom onset may be more beneficial than treatment initiated within seven days of symptom onset. A post hoc subgroup analysis within the prospective meta-analysis did not support this hypothesis. While some panel members believed that postponing systemic corticosteroids until after viral replication is contained by the immune system may be reasonable, many noted that, in practice, it is often impossible to ascertain symptom onset and that signs of severity often appear late (that is, denote a co-linearity between severity and timing). The panel concluded that, given the evidence, it was preferable to err on the side of administering corticosteroids when treating patients with severe or critical covid-19 (even if within 7 days of symptoms onset) and to err on the side of not giving corticosteroids when treating patients with non-severe disease (even if after 7 days of symptoms onset).

Evidence to decision

Benefits and harms

Substantial net benefits of the recommended alternative

Panel members who voted for a conditional recommendation argued that the trials evaluating systemic corticosteroids for COVID-19 reported limited information regarding potential harm. Between the two panel meetings, indirect evidence regarding the potential harmful effects of systemic corticosteroids from studies in sepsis, ARDS and community-acquired pneumonia (CAP) was added to the summary of findings table (66, 67). While generally of low certainty, these data were reassuring and suggested that corticosteroids are not associated with an increased risk of adverse events, beyond likely increasing the incidence of hyperglycaemia (moderate certainty evidence; absolute effect estimate 46 more per 1000 patients, 95% CI: 23 more to 72 more) and hypernatraemia (moderate certainty evidence; 26 more per 1000 patients, 95% CI: 13 more to 41 more). Panel members also noted that, given the expected effect of systemic corticosteroids on mortality, most patients would not refuse this intervention to avoid adverse events believed to be markedly less important to most patients than death.

In contrast with new agents proposed for COVID-19, clinicians have a vast experience of systemic corticosteroids and the panel was reassured by their overall safety profile. Moreover, the panel was confident that clinicians using these guidelines would be aware of additional potential side-effects and contraindications to systemic corticosteroid therapy, which may vary geographically in function of endemic microbiological flora. Notwithstanding, clinicians should exercise caution in use of corticosteroids in patients with diabetes or underlying immunocompromise.

Ultimately, the panel made its recommendation on the basis of the moderate certainty evidence of a 28-day mortality reduction of 8.7% in the critically ill and 6.7% in patients with severe COVID-19 who were not critically ill, respectively.

Preference and values

No substantial variability expected

The panel took an individual patient perspective to values and preferences but, given the burden of the pandemic for healthcare systems globally, also placed a high value on resource allocation and equity. The benefits of corticosteroids on mortality was deemed of critical importance to patients, with little or no anticipated variability in their preference to be offered treatment if severely ill from COVID-19.

Resources and other considerations

No important issues with the recommended alternative

Resource implications, feasibility, equity and human rights

In this guideline, the panel took an individual patient perspective, but also placed a high value on resource allocation. In such a perspective, attention is paid to the opportunity cost associated with the widespread provision of therapies for COVID-19. In contrast to other candidate treatments for COVID-19 that, generally, are expensive, often unlicensed, difficult to obtain and require advanced medical infrastructure, systemic corticosteroids are low cost, easy to administer, and readily available globally (57). Dexamethasone and prednisolone are among the most commonly listed medicines in national essential medicines lists; listed by 95% of countries. Dexamethasone was first listed by WHO as an essential medicine in 1977, while prednisolone was listed 2 years later (56).

Accordingly, systemic corticosteroids are among a relatively small number of interventions for COVID-19 that have the potential to reduce inequities and improve equity in health. Those considerations influenced the strength of this recommendation.

Acceptability

The ease of administration, the relatively short duration of a course of systemic corticosteroid therapy, and the generally benign safety profile of systemic corticosteroids for up to 7–10 days led the panel to conclude that the acceptability of this intervention was high.

Justification

This recommendation was achieved after a vote, which concerned the strength of the recommendation in favour of systemic corticosteroids. Of the 23 voting panel members, 19 (83%) voted in favour of a strong recommendation, and 4 (17%) voted in favour of a conditional recommendation. The reasons for the four cautionary votes, which were shared by some panel members who voted in favour of a strong recommendation, are summarized below.

Applicability

Panel members who voted for a conditional recommendation argued that many patients who were potentially eligible for the RECOVERY trial were excluded from participating in the evaluation of corticosteroids by their treating clinicians and that without detailed information on the characteristics of excluded patients, this precluded, in their opinion, a strong recommendation. Other panel members felt that such a proportion of excluded patients was the norm rather than the exception in pragmatic trials and that, while detailed information on the reasons for excluding patients were not collected, the main reasons for refusing to offer participation in the trial were likely related to safety concerns of stopping corticosteroids in patients with a clear indication for corticosteroids (confirmed as per personal communication from the RECOVERY Principal Investigator). Panel members noted that there are few absolute contraindications to a 7–10 day course of corticosteroid therapy, that recommendations are intended for the average patient population, and that it is understood that even strong recommendations should not be applied to patients in whom the intervention is contraindicated as determined by the treating clinician.

Eventually, the panel concluded that this recommendation applies to patients with severe and critical COVID-19 regardless of hospitalization status. The underlying assumption is that these patients would be treated in hospitals and receive respiratory support in the form of oxygen; non-invasive or invasive ventilation if these options were available. Following GRADE guidance, in making a strong recommendation, the panel has inferred that all or almost all fully informed patients with severe COVID-19 would choose to take systemic corticosteroids. It is understood that even in the context of a strong recommendation, the intervention may be contraindicated for certain patients. Absolute contraindications for 7–10 day courses of systemic corticosteroid therapy are rare. In considering potential contraindications, clinicians must determine if they warrant depriving a patient of a potentially life-saving therapy.

The applicability of the recommendation is less clear for populations that were under-represented in the considered trials, such as children, patients with tuberculosis, and those who are immunocompromised. Notwithstanding, clinicians will also consider the risk of depriving these patients of potentially life-saving therapy. In contrast, the panel concluded that the recommendation should definitely be applied to certain patients who were not included in the trials, such as patients with severe and critical COVID-19 who could not be hospitalized or receive oxygen because of resource limitations.

The recommendation does not apply to the following uses of corticosteroids: transdermal or inhaled administration, high-dose or long-term regimens, or prophylaxis.

Clinical question/ PICO

Population: Patients with critical COVID-19
Intervention: Steroids
Comparator: Standard Care

Summary

Outline of the evidence on systemic corticosteroids

While six trials evaluated systemic corticosteroids exclusively in critically ill patients, the RECOVERY trial enrolled hospitalized patients with covid-19 and reported mortality data by subgroup, whereas the smaller GLUCOCOVID trial, which also enrolled hospitalized, patients did not. The panel considered the results of a subgroup analysis of the RECOVERY trial suggesting that the relative effects of systemic corticosteroids varied as a function of the level of respiratory support received at randomization. On the basis of the peer-reviewed criteria for credible subgroup effects (42), the panel determined that the subgroup effect was sufficiently credible to warrant separate recommendations for severe and non-severe covid-19.

Population - There were data from 1703 critically ill patients in seven trials. RECOVERY, the largest of the seven trials randomized 6425 hospitalized patients in the United Kingdom (2104 were randomized to dexamethasone and 4321 were randomized to usual care). At the time of randomization, 16% were receiving invasive mechanical ventilation or extracorporeal membrane oxygenation, 60% were receiving oxygen only (with or without non-invasive ventilation), and 24% were receiving neither (12). The mortality data from six other smaller trials included approximately 700 critically ill patients (definitions of critical illness varied across studies) enrolled up to 9 June 2020, approximately four-fifths were invasively mechanically ventilated; approximately one-half were randomized to receive corticosteroid therapy, and one-half randomized to no corticosteroid therapy. For patients with severe and non-severe covid-19, data was only available by relevant subgroup in RECOVERY (3883 patients with severe and 1535 patients with non-severe covid-19). Because the mortality data from one trial (GLUCOCOVID, n=63) was not reported separately for severe and non-severe covid-19 [68], the panel reviewed only the data pertaining to the outcome of mechanical ventilation from this trial.

Interventions - RECOVERY evaluated the effects of dexamethasone 6 mg given once daily (oral or intravenous) for up to 10 days. Other corticosteroid regimens included: dexamethasone 20 mg daily for 5 days followed by 10 mg daily for 5 days (two trials, DEXA-COVID, CoDEX); hydrocortisone 200 mg daily for 4 to 7 days followed by 100 mg daily for 2 to 4 days and then 50 mg daily for 2 to 3 days (one trial, CAPE-COVID); hydrocortisone 200 mg daily for 7 days (one trial, REMAP-CAP); methylprednisolone 40 mg every 12 hours for 5 days (one trial, Steroids-SARI); and methylprednisolone 40 mg every 12 hours for 3 days and then 20 mg every 12 hours for 3 days (one trial, GLUCOCOVID) (3). Seven of the trials were conducted in individual countries (Brazil, China, Denmark, France, Spain) whilst REMAP-CAP was an international study (recruiting in 14 European countries, Australia, Canada, New Zealand, Saudi Arabia and United Kingdom).

Outcomes - All trials reported mortality 28 days after randomization, except for one trial at 21 days and the another at 30 days.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Plain text summary
		Standard Care	Steroids		
Mortality 28 days	Relative risk 0.79 (CI 95% 0.7 - 0.9) Based on data from 1,703 patients in 7 studies. Follow up: 28 days.	415 per 1000	328 per 1000	Moderate Due to serious risk of bias ¹	Systemic corticosteroids probably reduce the risk of 28-day mortality in patients with critical illness due to COVID-19.
		Difference: 87 fewer per 1000 (CI 95% 124 fewer - 41 fewer)			

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Plain text summary
		Standard Care	Steroids		
Need for invasive mechanical ventilation 28 days	Relative risk 0.74 (CI 95% 0.59 - 0.93) Based on data from 5,481 patients in 2 studies. Follow up: 28 days.	116 per 1000	86 per 1000	Moderate Due to serious risk of bias ²	Systemic corticosteroids probably reduce the need of mechanical ventilation
Gastrointestinal bleeding	Relative risk 1.06 (CI 95% 0.85 - 1.33) Based on data from 5,403 patients in 30 studies.	48 per 1000	51 per 1000	Low Due to serious indirectness, Due to serious imprecision ³	Corticosteroids may not increase the risk of gastrointestinal bleeding.
Super-infections	Relative risk 1.01 (CI 95% 0.9 - 1.13) Based on data from 6,027 patients in 32 studies.	186 per 1000	188 per 1000	Low Due to serious indirectness, Due to serious imprecision ⁴	Corticosteroids may not increase the risk of super-infections.
Hyperglycaemia	Relative risk 1.16 (CI 95% 1.08 - 1.25) Based on data from 8,938 patients in 24 studies.	286 per 1000	332 per 1000	Moderate Due to serious indirectness ⁵	Corticosteroids probably increase the risk of hyperglycaemia.
Hypernatremia	Relative risk 1.64 (CI 95% 1.32 - 2.03) Based on data from 5,015 patients in 6 studies.	40 per 1000	66 per 1000	Moderate Due to serious indirectness ⁶	Corticosteroids probably increase the risk of hypernatremia.
Neuromuscular weakness	Relative risk 1.09 (CI 95% 0.86 - 1.39) Based on data from 6,358 patients in 8 studies.	69 per 1000	75 per 1000	Low Due to serious indirectness, Due to serious imprecision ⁷	Corticosteroids may not increase the risk of neuromuscular weakness.
Neuropsychiatric effects	Relative risk 0.81 (CI 95% 0.41 - 1.63) Based on data from 1,813 patients in 7 studies.	35 per 1000	28 per 1000	Low Due to serious indirectness, Due to serious imprecision ⁸	Corticosteroids may not increase the risk of neuropsychiatric effects.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Plain text summary
		Standard Care	Steroids		
Duration of hospitalization	Measured by: days Lower better Based on data from: 6,425 patients in 1 studies. (Randomized controlled)	13 days	12 days	Low Due to serious risk of bias, Due to serious imprecision ⁹	Steroids may result in an important reduction in the duration of hospitalizations

1. **Risk of bias: Serious.** lack of blinding. **Inconsistency: No serious.** **Indirectness: No serious.** **Imprecision: No serious.** **Publication bias: No serious.**
2. **Risk of bias: Serious.** lack of blinding. **Inconsistency: No serious.** **Indirectness: No serious.** **Imprecision: No serious.** **Publication bias: No serious.**
3. **Inconsistency: No serious.** **Indirectness: Serious.** **Imprecision: Serious.** **Publication bias: No serious.**
4. **Inconsistency: No serious.** **Indirectness: Serious.** **Imprecision: Serious.** **Publication bias: No serious.**
5. **Indirectness: Serious.**
6. **Indirectness: Serious.**
7. **Indirectness: Serious.** **Imprecision: Serious.**
8. **Indirectness: Serious.** **Imprecision: Serious.**
9. **Risk of bias: Serious.** lack of blinding. **Inconsistency: No serious.** **Indirectness: No serious.** **Imprecision: Serious.** confidence interval includes no benefit. **Publication bias: No serious.**

Clinical question/ PICO

Population: Patients with severe COVID-19
Intervention: Steroids
Comparator: Standard Care

Summary

Outline of the evidence on systemic corticosteroids

While six trials evaluated systemic corticosteroids exclusively in critically ill patients, the RECOVERY trial enrolled hospitalized patients with covid-19 and reported mortality data by subgroup, whereas the smaller GLUCOCOVID trial, which also enrolled hospitalized, patients did not. The panel considered the results of a subgroup analysis of the RECOVERY trial suggesting that the relative effects of systemic corticosteroids varied as a function of the level of respiratory support received at randomization. On the basis of the peer-reviewed criteria for credible subgroup effects (42), the panel determined that the subgroup effect was sufficiently credible to warrant separate recommendations for severe and non-severe covid-19.

Population - There were data from 1703 critically ill patients in seven trials. RECOVERY, the largest of the seven trials randomized 6425 hospitalized patients in the United Kingdom (2104 were randomized to dexamethasone and 4321 were randomized to usual care). At the time of randomization, 16% were receiving invasive mechanical ventilation or extracorporeal membrane oxygenation, 60% were receiving oxygen only (with or without non-invasive ventilation), and 24% were receiving neither (12). The mortality data from six other smaller trials included approximately 700 critically ill patients (definitions of critical illness varied across studies) enrolled up to 9 June 2020, approximately four-fifths were invasively mechanically ventilated; approximately one-half were randomized to receive corticosteroid therapy, and one-half randomized to no corticosteroid therapy. For patients with severe and non-severe covid-19, data was only available by relevant subgroup in RECOVERY (3883 patients with severe and 1535 patients with non-severe covid-19). Because the mortality data from one trial (GLUCOCOVID, n=63) was not reported separately for severe and non-severe covid-19

(68), the panel reviewed only the data pertaining to the outcome of mechanical ventilation from this trial.
Interventions – RECOVERY evaluated the effects of dexamethasone 6 mg given once daily (oral or intravenous) for up to 10 days. Other corticosteroid regimens included: dexamethasone 20 mg daily for 5 days followed by 10 mg daily for 5 days (two trials, DEXA-COVID, CoDEX); hydrocortisone 200 mg daily for 4 to 7 days followed by 100 mg daily for 2 to 4 days and then 50 mg daily for 2 to 3 days (one trial, CAPE-COVID); hydrocortisone 200 mg daily for 7 days (one trial, REMAP-CAP); methylprednisolone 40 mg every 12 hours for 5 days (one trial, Steroids-SARI); and methylprednisolone 40 mg every 12 hours for 3 days and then 20 mg every 12 hours for 3 days (one trial, GLUCOCOVID) (3). Seven of the trials were conducted in individual countries (Brazil, China, Denmark, France, Spain) whilst REMAP-CAP was an international study (recruiting in 14 European countries, Australia, Canada, New Zealand, Saudi Arabia and United Kingdom).
Outcomes - All trials reported mortality 28 days after randomization, except for one trial at 21 days and the another at 30 days.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Plain text summary
		Standard Care	Steroids		
Mortality 28 days	Relative risk 0.8 (CI 95% 0.7 - 0.92) Based on data from 3,883 patients in 1 studies. Follow up: 28 days.	334 per 1000	267 per 1000	Moderate Due to serious risk of bias ¹	Systemic corticosteroids probably reduce the risk of 28-day mortality in patients with severe COVID-19.
Need for invasive mechanical ventilation 28 days	Relative risk 0.74 (CI 95% 0.59 - 0.93) Based on data from 5,481 patients in 2 studies. Follow up: 28 days.	116 per 1000	86 per 1000	Moderate Due to serious risk of bias ²	Systemic corticosteroids probably reduce the need for mechanical ventilation
Gastrointestinal bleeding	Relative risk 1.06 (CI 95% 0.85 - 1.33) Based on data from 5,403 patients in 30 studies.	48 per 1000	51 per 1000	Low Due to serious indirectness, Due to serious imprecision ³	Corticosteroids may not increase the risk of gastrointestinal bleeding.
Super-infections	Relative risk 1.01 (CI 95% 0.9 - 1.13) Based on data from 6,027 patients in 32 studies.	186 per 1000	188 per 1000	Low Due to serious indirectness, Due to serious imprecision ⁴	Corticosteroids may not increase the risk of super-infections.
Hyperglycaemia	Relative risk 1.16 (CI 95% 1.08 - 1.25) Based on data from 8,938 patients in 24 studies.	286 per 1000	332 per 1000	Moderate Due to serious indirectness ⁵	Corticosteroids probably increase the risk of hyperglycaemia.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Plain text summary
		Standard Care	Steroids		
		(CI 95% 23 more - 72 more)			
Hypernatremia	Relative risk 1.64 (CI 95% 1.32 - 2.03) Based on data from 5,015 patients in 6 studies.	40 per 1000	66 per 1000	Moderate Due to serious indirectness ⁶	Corticosteroids probably increase the risk of hypernatremia.
Neuromuscular weakness	Relative risk 1.09 (CI 95% 0.86 - 1.39) Based on data from 6,358 patients in 8 studies.	69 per 1000	75 per 1000	Low Due to serious indirectness, Due to serious imprecision ⁷	Corticosteroids may not increase the risk of neuromuscular weakness.
Neuropsychiatric effects	Relative risk 0.81 (CI 95% 0.41 - 1.63) Based on data from 1,813 patients in 7 studies.	35 per 1000	28 per 1000	Low Due to serious indirectness, Due to serious imprecision ⁸	Corticosteroids may not increase the risk of neuropsychiatric effects.
Duration of hospitalization	Measured by: days Lower better Based on data from: 6,425 patients in 1 studies. (Randomized controlled)	13 days	12 days	Low Due to serious risk of bias, Due to serious imprecision ⁹	Steroids may result in an important reduction in the duration of hospitalizations
		CI 95%			

1. Risk of bias: Serious. lack of blinding. Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.
2. Risk of bias: Serious. lack of blinding. Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.
3. Inconsistency: No serious. Indirectness: Serious. Imprecision: Serious. Publication bias: No serious.
4. Inconsistency: No serious. Indirectness: Serious. Imprecision: Serious. Publication bias: No serious.
5. Indirectness: Serious.
6. Indirectness: Serious.
7. Indirectness: Serious. Imprecision: Serious.
8. Indirectness: Serious. Imprecision: Serious.
9. Risk of bias: Serious. lack of blinding. Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious. confidence interval includes no benefit. Publication bias: No serious.

For patients with non-severe COVID-19 infection (absence of criteria for severe or critical infection)

Conditional recommendation against

We suggest not to use corticosteroids.

Practical info

With the conditional recommendation against the use of corticosteroids in patients with non-severe COVID-19 the following practical information apply in situations where such treatment is to be considered:

Route Systemic corticosteroids may be administered both orally and intravenously. Of note, while the bioavailability of dexamethasone is very high (i.e. similar concentrations are achieved in plasma after oral and intravenous intake), critically ill patients may be unable to absorb any nutrients or medications due to intestinal dysfunction. Clinicians therefore may consider administering systemic corticosteroids intravenously rather than orally if intestinal dysfunction is suspected.

Duration While more patients received corticosteroids in the form of dexamethasone 6 mg daily for up to 10 days, the total duration of regimens evaluated in the seven trials varied between 5 and 14 days, and treatment was generally discontinued at hospital discharge (i.e. the duration of treatment could be less than the duration stipulated in the protocols).

Dose The once daily dexamethasone formulation may increase adherence. A dose of 6 mg of dexamethasone is equivalent (in terms of glucocorticoid effect) to 150 mg of hydrocortisone (e.g. 50 mg every 8 hours), or 40 mg of prednisone, or 32 mg of methylprednisolone (e.g. 8 mg every 6 hours or 16 mg every 12 hours). It would be prudent to monitor glucose levels in patients with severe and critical COVID-19, regardless of whether the patient is known to have diabetes.

Timing The timing of therapy from onset of symptoms was discussed by the panel. The RECOVERY investigators reported a subgroup analysis suggesting that the initiation of therapy 7 days or more after symptom onset may be more beneficial than treatment initiated within 7 days of treatment onset. A post hoc subgroup analysis within the PMA did not support this hypothesis. While some panel members believed that postponing systemic corticosteroids until after viral replication is contained by the immune system may be reasonable, many noted that, in practice, it is often impossible to ascertain symptom onset and that signs of severity frequently appear late (i.e. denote a co-linearity between severity and timing). The panel concluded that, given the evidence, it was preferable to err on the side of administering corticosteroids when treating patients with severe or critical COVID-19 (even if within 7 days of symptoms onset) and to err on the side of not giving corticosteroids when treating patients with non-severe disease (even if after 7 days of symptoms onset).

Other endemic infections that may worsen with corticosteroids should be considered. For example, for *Strongyloides stercoralis* hyperinfection associated with corticosteroid therapy, diagnosis or empiric treatment may be considered in endemic areas if steroids are used.

Evidence to decision

Benefits and harms

The panel made its recommendation on the basis of low certainty evidence suggesting a potential increase of 3.9% in 28-day mortality among patients with COVID-19 who are not severely ill. The certainty of the evidence for this specific subgroup was downgraded due to serious imprecision (i.e. the evidence does not allow to rule out a mortality reduction) and risk of bias due to lack of blinding. In making a conditional recommendation against the indiscriminate use of systemic corticosteroids, the panel inferred that most fully informed individuals with non-severe illness would not want to receive systemic corticosteroids, but many could want to consider this intervention through shared decision-making with their treating physician (6).

Note: WHO recommends antenatal corticosteroid therapy for pregnant women at risk of preterm birth from 24 to 34 weeks' gestation when there is no clinical evidence of maternal infection, and adequate childbirth and newborn care is available. However, in cases where the woman presents with mild or moderate COVID-19, the clinical benefits of antenatal

corticosteroid might outweigh the risks of potential harm to the mother. In this situation, the balance of benefits and harms for the woman and the preterm newborn should be discussed with the woman to ensure an informed decision, as this assessment may vary depending on the woman's clinical condition, her wishes and that of her family, and available health care resources.

Preference and values

The weak or conditional recommendation was driven by likely variation in patient values and preferences. The panel judged that most individuals with non-severe illness would decline systemic corticosteroids. However, many may want them after shared decision making with their treating physician.

Resources and other considerations

Resource implications, feasibility, equity and human rights

The panel also considered that in order to help guarantee access to systemic corticosteroids for patients with severe and critical COVID-19, it is reasonable to avoid administering this intervention to patients who, given the current evidence, would not appear to derive any benefit from this intervention.

Justification

This recommendation was achieved by consensus.

Applicability

This recommendation applies to patients with non-severe disease regardless of their hospitalization status. The panel noted that patients with non-severe COVID-19 would not normally require acute care in hospital or respiratory support, but that in some jurisdictions, these patients may be hospitalized for isolation purposes only, in which case they should not be treated with systemic corticosteroids. The panel concluded that systemic corticosteroids should not be stopped for patients with non-severe COVID-19 who are already treated with systemic corticosteroids for other reasons (e.g. patients with chronic obstructive pulmonary disease need not discontinue a course of systemic oral corticosteroids; or other chronic autoimmune diseases). If the clinical condition of patients with non-severe COVID-19 worsens (i.e. increase in respiratory rate, signs of respiratory distress or hypoxaemia) they should receive systemic corticosteroids (see recommendation 1).

Clinical question/ PICO

Population:	Patients with non-severe COVID-19
Intervention:	Steroids
Comparator:	Standard Care

Summary

Outline of the evidence on systemic corticosteroids

While six trials evaluated systemic corticosteroids exclusively in critically ill patients, the RECOVERY trial enrolled hospitalized patients with covid-19 and reported mortality data by subgroup, whereas the smaller GLUCOCOVID trial, which also enrolled hospitalized, patients did not. The panel considered the results of a subgroup analysis of the RECOVERY trial suggesting that the relative effects of systemic corticosteroids varied as a function of the level of respiratory support received at randomization. On the basis of the peer-reviewed criteria for credible subgroup effects (42), the panel determined that the subgroup effect was sufficiently credible to warrant separate recommendations for severe and non-severe covid-19.

Population - There were data from 1703 critically ill patients in seven trials. RECOVERY, the largest of the seven trials randomized 6425 hospitalized patients in the United Kingdom (2104 were randomized to dexamethasone and 4321

were randomized to usual care). At the time of randomization, 16% were receiving invasive mechanical ventilation or extracorporeal membrane oxygenation, 60% were receiving oxygen only (with or without non-invasive ventilation), and 24% were receiving neither (12). The mortality data from six other smaller trials included approximately 700 critically ill patients (definitions of critical illness varied across studies) enrolled up to 9 June 2020, approximately four-fifths were invasively mechanically ventilated; approximately one-half were randomized to receive corticosteroid therapy, and one-half randomized to no corticosteroid therapy. For patients with severe and non-severe covid-19, data was only available by relevant subgroup in RECOVERY (3883 patients with severe and 1535 patients with non-severe covid-19). Because the mortality data from one trial (GLUCOCOVID, n=63) was not reported separately for severe and non-severe covid-19 (68), the panel reviewed only the data pertaining to the outcome of mechanical ventilation from this trial.

Interventions – RECOVERY evaluated the effects of dexamethasone 6 mg given once daily (oral or intravenous) for up to 10 days. Other corticosteroid regimens included: dexamethasone 20 mg daily for 5 days followed by 10 mg daily for 5 days (two trials, DEXA-COVID, CoDEX); hydrocortisone 200 mg daily for 4 to 7 days followed by 100 mg daily for 2 to 4 days and then 50 mg daily for 2 to 3 days (one trial, CAPE-COVID); hydrocortisone 200 mg daily for 7 days (one trial, REMAP-CAP); methylprednisolone 40 mg every 12 hours for 5 days (one trial, Steroids-SARI); and methylprednisolone 40 mg every 12 hours for 3 days and then 20 mg every 12 hours for 3 days (one trial, GLUCOCOVID) (3) Seven of the trials were conducted in individual countries (Brazil, China, Denmark, France, Spain) whilst REMAP-CAP was an international study (recruiting in 14 European countries, Australia, Canada, New Zealand, Saudi Arabia and United Kingdom).

Outcomes - All trials reported mortality 28 days after randomization, except for one trial at 21 days and the another at 30 days.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Plain text summary
		Standard Care	Steroids		
Mortality 28 days	Relative risk 1.22 (CI 95% 0.93 - 1.61) Based on data from 1,535 patients in 1 studies. Follow up: 28 days.	176 per 1000	215 per 1000	Low Due to serious risk of bias, Due to serious imprecision ¹	Systemic corticosteroids may increase the risk of 28-day mortality in patients with non-severe COVID-19
Need for invasive mechanical ventilation 28 days	Relative risk 0.74 (CI 95% 0.59 - 0.93) Based on data from 5,481 patients in 2 studies. Follow up: 28 days.	116 per 1000	86 per 1000	Moderate Due to serious risk of bias ²	Systemic corticosteroids probably reduce the need for mechanical ventilation
Duration of hospitalization	Based on data from 6,425 patients in 1 studies. Follow up: NR.	13	12	Low Due to serious risk of bias, Due to serious imprecision ³	Steroids may result in an important reduction in the duration of hospitalizations
Gastrointestinal bleeding	Relative risk 1.06 (CI 95% 0.85 - 1.33) Based on data from 5,403 patients in 30	48 per 1000	51 per 1000	Low Due to serious indirectness, Due to serious	Corticosteroids may not increase the risk of gastrointestinal bleeding.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the evidence (Quality of evidence)	Plain text summary
		Standard Care	Steroids		
	studies.	Difference: 3 more per 1000 (CI 95% 7 fewer - 16 more)		imprecision ⁴	
Super-infections	Relative risk 1.01 (CI 95% 0.9 - 1.13) Based on data from 6,027 patients in 32 studies.	186 per 1000	188 per 1000	Low Due to serious indirectness, Due to serious imprecision ⁵	Corticosteroids may not increase the risk of super-infections.
		Difference: 2 more per 1000 (CI 95% 19 fewer - 24 more)			
Hyperglycaemia	Relative risk 1.16 (CI 95% 1.08 - 1.25) Based on data from 8,938 patients in 24 studies.	286 per 1000	332 per 1000	Moderate Due to serious indirectness ⁶	Corticosteroids probably increase the risk of hyperglycaemia.
		Difference: 46 more per 1000 (CI 95% 23 more - 72 more)			
Hypernatremia	Relative risk 1.64 (CI 95% 1.32 - 2.03) Based on data from 5,015 patients in 6 studies.	40 per 1000	66 per 1000	Moderate Due to serious indirectness ⁷	Corticosteroids probably increase the risk of hypernatremia.
		Difference: 26 more per 1000 (CI 95% 13 more - 41 more)			
Neuromuscular weakness	Relative risk 1.09 (CI 95% 0.86 - 1.39) Based on data from 6,358 patients in 8 studies.	69 per 1000	75 per 1000	Low Due to serious indirectness, Due to serious imprecision ⁸	Corticosteroids may not increase the risk of neuromuscular weakness.
		Difference: 6 more per 1000 (CI 95% 10 fewer - 27 more)			
Neuropsychiatric effects	Relative risk 0.81 (CI 95% 0.41 - 1.63) Based on data from 1,813 patients in 7 studies.	35 per 1000	28 per 1000	Low Due to serious indirectness, Due to serious imprecision ⁹	Corticosteroids may not increase the risk of neuropsychiatric effects.
		Difference: 7 fewer per 1000 (CI 95% 21 fewer - 22 more)			
Duration of hospitalization	Measured by: days Lower better Based on data from: 6,425 patients in 1 studies. (Randomized controlled)	13 days	12 days	Low Due to serious risk of bias, Due to serious imprecision ¹⁰	Steroids may result in an important reduction in the duration of hospitalizations
		CI 95%			

1. Risk of bias: Serious. lack of blinding. Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious. Publication bias: No serious.

2. Risk of bias: Serious. lack of blinding. Inconsistency: No serious. Indirectness: No serious. Imprecision: No serious.

Publication bias: No serious.

3. **Risk of bias: Serious.** lack of blinding. **Inconsistency: No serious.** **Indirectness: No serious.** **Imprecision: Serious.** confidence interval includes no benefit. **Publication bias: No serious.**
4. **Inconsistency: No serious.** **Indirectness: Serious.** **Imprecision: Serious.** **Publication bias: No serious.**
5. **Inconsistency: No serious.** **Indirectness: Serious.** **Imprecision: Serious.** **Publication bias: No serious.**
6. **Indirectness: Serious.**
7. **Indirectness: Serious.**
8. **Indirectness: Serious.** **Imprecision: Serious.**
9. **Indirectness: Serious.** **Imprecision: Serious.**
10. **Risk of bias: Serious.** lack of blinding. **Inconsistency: No serious.** **Indirectness: No serious.** **Imprecision: Serious.** confidence interval includes no benefit. **Publication bias: No serious.**

8. Uncertainties, emerging evidence and future research

The guideline recommendations for COVID-19 therapeutics demonstrate remaining uncertainties concerning treatment effects for all outcomes of importance to patients. There is also a need for better evidence on prognosis and values and preferences of patients with COVID-19 infection. Here we outline key uncertainties for ivermectin identified by the GDG, adding to those for corticosteroids, remdesivir and hydroxychloroquine and lopinavir/ritonavir in previous versions of the living guideline. These uncertainties may inform future research, i.e. the production of more relevant and reliable evidence to inform policy and practice. We also outline emerging evidence in the rapidly changing landscape of trials for COVID-19.

Ongoing uncertainties and opportunities for future research

Ivermectin

Given the very low certainty in estimates for most critical outcomes of interest, the GDG felt that further high-quality clinical trials examining this drug would be essential before any recommendation for use as part of clinical care. This includes further RCTs examining both inpatients and outpatients and those with varying disease severities and using different ivermectin dosing regimens. The focus of these studies should be on outcomes important to patients such as mortality, quality of life, need for hospitalization, need for invasive mechanical ventilation and time to clinical or symptom improvement. Also, a better characterization of potential harms with ivermectin in patients with COVID-19 would be important.

Hydroxychloroquine

Although some uncertainty remains, the GDG panel felt that further research was unlikely to uncover a subgroup of patients that benefit from hydroxychloroquine on the most important outcomes (mortality, mechanical ventilation) given the consistent results in trials across disease severity and location.

Lopinavir/ritonavir

Although some uncertainty remains, the GDG panel felt that further research was unlikely to uncover a subgroup of patients that benefit from hydroxychloroquine on the most important outcomes (mortality, mechanical ventilation) given the consistent results in trials across disease severity and location.

Remdesivir and effects on

- critical outcomes of interest, particularly those that impact resource allocation, such as the need for mechanical ventilation, duration of mechanical ventilation and duration of hospitalization;
- specific subgroups, such as different severities of illness, different time (days) since onset of illness, children and older adults, pregnant women, and duration of therapy;
- long-term outcomes such as mortality at extended endpoints or long-term quality of life;
- long-term safety and rare but important side-effects;
- patient-reported outcomes such as symptom burden;
- outcomes, when used in combination with other agents, such as, but not limited to, corticosteroids;
- impact on viral shedding, viral clearance, patient infectivity.

Corticosteroids and effects on

- long-term mortality and functional outcomes in COVID-19 survivors;
- patients with non-severe COVID-19 (i.e. pneumonia without hypoxaemia);
- outcomes, when used in combination with additional therapies for COVID-19, such as novel immunomodulators. It will become increasingly important to ascertain how these interact with systemic corticosteroids. All investigational therapies for severe and critical COVID-19 (including remdesivir) should be compared with systemic corticosteroids or evaluated in combination with systemic corticosteroids vs systemic corticosteroids alone;
- immunity and the risk of a subsequent infection, which may impact the risk of death after 28 days;
- outcomes, by different steroid preparation, dosing and optimal timing of drug initiation.

Emerging evidence

The unprecedented volume of planned and ongoing studies for COVID-19 interventions – over 3000 RCTs as of 1 March 2021 – implies that more reliable and relevant evidence will emerge to inform policy and practice (11). An overview of registered and ongoing trials for COVID-19 therapeutics and prophylaxis is available from the [Infectious Diseases Data Observatory](#), through their living

systematic review of COVID-19 clinical trial registrations (11), the WHO website and other repositories, such as the [COVID-NMA initiative](#).

Whereas most of these studies are small and of variable methodological quality, a number of large, international platform trials (e.g. RECOVERY, SOLIDARITY and DISCOVERY) are better equipped to provide robust evidence for a number of potential treatment options (10). Such trials can also adapt their design, recruitment strategies and selection of interventions based on new insights, exemplified by the uncertainties outlined above.

Concerning ivermectin used to treat COVID-19, more than 66 RCTs planning to enrol more than 12 000 participants (range 24 - 2724) are registered or ongoing (11).

9. Authorship, contributions, acknowledgements

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WHO Therapeutics Steering Committee

The committee includes representatives from various WHO departments at headquarters and the regions and has been approved by the WHO Director of the Country Readiness Department, and the WHO Chief Scientist. The WHO Secretariat meets on a regular basis to discuss when to trigger guideline updates based on evidence updates from the WHO rapid review team, and other sources of evidence and selects the members of the **Guideline Development Group (GDG)** for living guidance.

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The WHO Therapeutics Steering Committee is fully responsible for decisions about guidance production and convening the GDG.

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