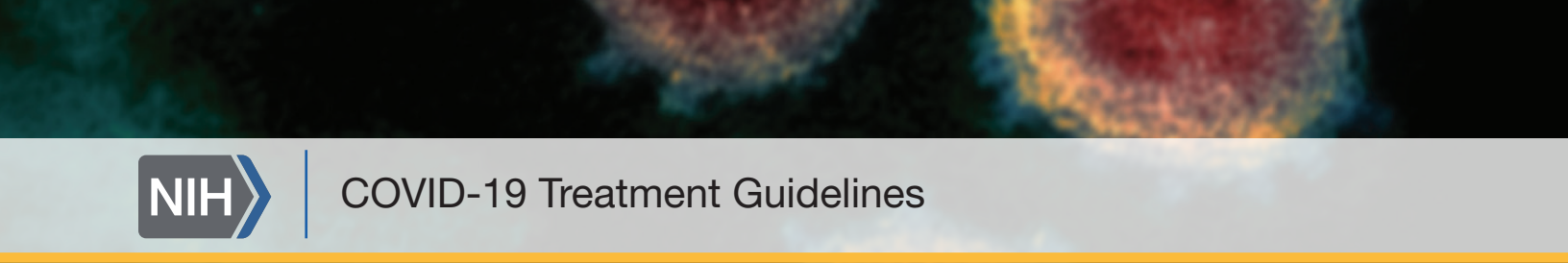

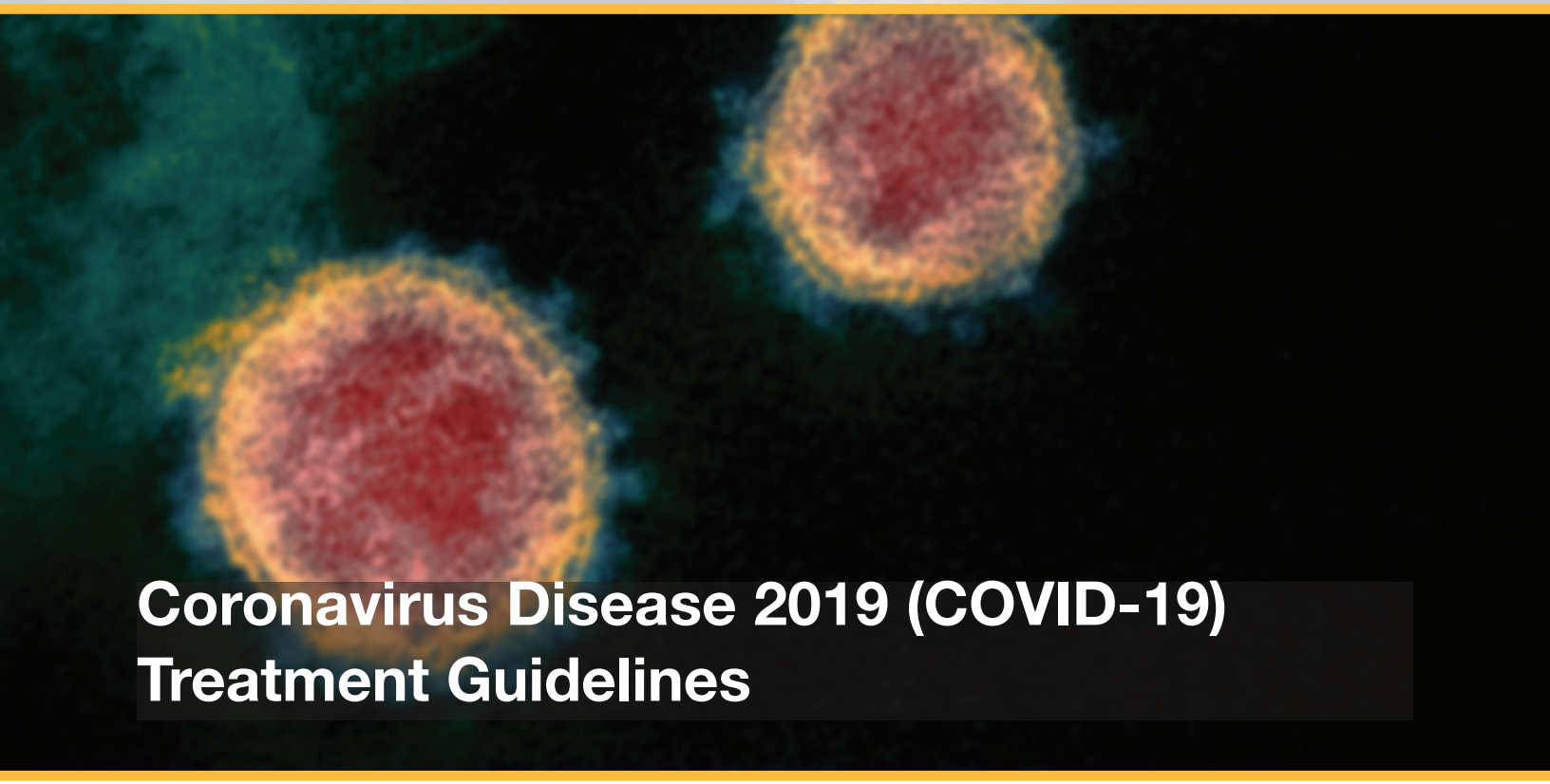

Coronavirus Disease 2019 (COVID-19) Treatment Guidelines

How to Cite the COVID-19 Treatment Guidelines:

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

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

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Table of Contents

What's New in the Guidelines

(Last updated June 25, 2020)

June 25, 2020 Update: Based on a preliminary analysis of the data from the Randomised Evaluation of COVID-19 Therapy (RECOVERY) study, the COVID-19 Treatment Guidelines Panel (the Panel) developed recommendations for the use of the corticosteroid dexamethasone in people with COVID-19.

This new guidance from the Panel includes the rationale for these recommendations and additional factors for clinicians to consider before administering dexamethasone to people with COVID-19. For more information, please visit the full announcement.

June 16, 2020 Update: On June 15, The Food and Drug Administration revoked the emergency use authorization (EUA) that permitted the use of chloroquine and hydroxychloroquine donated to the Strategic National Stockpile to treat certain patients with COVID-19. In light of this announcement, the following sections of the COVID-19 Treatment Guidelines have been updated to remove the information regarding the EUA:

- Antiviral Drugs Under Investigation
- Chloroquine or Hydroxychloroquine
- Table 2b

Key Updates to the Guidelines

Special Considerations in Children

This section now includes a preliminary description of multisystem inflammatory syndrome in children (MIS-C), a condition that has been associated with COVID-19 in children and young adults. This section will be updated as more data become available.

Potential Antiviral Drugs Under Evaluation for the Treatment of COVID-19

The recommendations for using remdesivir, chloroquine, and hydroxychloroquine to treat COVID-19 have been revised based on data from recently published clinical trials and observational cohort studies. This section and Table 2a now include detailed summaries of the study results. The revised recommendations are listed below, and the rationale for these recommendations is discussed in the text.

Remdesivir

Recommendation for Hospitalized Patients with Severe COVID-19:

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends the investigational antiviral agent remdesivir for treatment of COVID-19 in hospitalized patients with SpO_2 ≤94% on ambient air (at sea level) or those who require supplemental oxygen **(AI)**.
- The Panel recommends remdesivir for treatment of COVID-19 in patients who are on mechanical ventilation or extracorporeal membrane oxygenation (ECMO) **(BI)**.

Recommendation for Duration of Therapy in Patients with Severe COVID-19 Who Are Not Intubated:

- The Panel recommends that hospitalized patients with severe COVID-19 who are not intubated receive 5 days of remdesivir **(AI)**.

Recommendation for Duration of Therapy for Mechanically Ventilated Patients, Patients on ECMO, or Patients Who Have Not Shown Adequate Improvement After 5 Days of Therapy:

- There are insufficient data on the optimal duration of therapy for mechanically ventilated patients, patients on ECMO, or patients who have not shown adequate improvement after 5 days of therapy. In these groups, some experts extend the total remdesivir treatment duration to up to 10 days **(CIII)**.

Recommendation for Patients with Mild or Moderate COVID-19:

- There are insufficient data for the Panel to recommend for or against remdesivir for the treatment of patients with mild or moderate COVID-19.

Chloroquine or Hydroxychloroquine

- The Panel **recommends against** the use of chloroquine or hydroxychloroquine for the treatment of COVID-19, except in a clinical trial **(AII)**.

New Sections of the Guidelines

Acute Kidney Injury and Renal Replacement Therapy

In this new subsection of Care of Critically Ill Patients with COVID-19, the Panel recommends continuous renal replacement therapy (CRRT) in critically ill patients with COVID-19 who have acute kidney injury and who develop indications for renal replacement therapy **(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)**. The primary rationale for these recommendations is to reduce the risk of transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to health care workers, since there is no evidence that one modality is more beneficial than another.

Testing for SARS-CoV-2 Infection

This section was added to discuss the use of virologic and serologic testing for SARS-CoV-2. This section includes:

- Information on virologic testing (i.e., molecular diagnostic and antigen testing for SARS-CoV-2), with the following recommendation:
  - The Panel recommends that a molecular or antigen test for SARS-CoV-2 should be used to diagnose acute SARS-CoV-2 infection **(AIII)**.
- New information on the role of serologic testing in diagnosing and screening for COVID-19. Current serologic assays have limitations in their performance and their ability to determine whether a patient is immune to SARS-CoV-2 infection. In light of these limitations, the Panel:
  - **Recommends against** the use of serologic testing as the sole basis for diagnosis of acute SARS-CoV-2 infection **(AIII)**.
  - **Recommends against** the use of serologic testing to determine whether a person is immune to SARS-CoV-2 infection **(AIII)**.

Additional Updates to the Guidelines

Oxygenation and Ventilation

In this section, the Panel added the following recommendations for the use of awake prone positioning in critically ill patients who are not intubated:

- 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 **(CIII)**.
- The Panel **recommends against** using awake prone positioning as a rescue therapy for refractory hypoxemia to avoid intubation in patients who otherwise require intubation and mechanical ventilation **(AIII)**.

Interleukin-1 Inhibitors

New clinical data from a single-center case series and a single-center retrospective cohort study that evaluated the use of anakinra to treat of COVID-19 have been added. There is no change to the Panel's recommendation for interleukin-1 inhibitors.

Interleukin-6 Inhibitors

New clinical data from a prospective, open-label study of tocilizumab have been added. There is no change to the Panel's recommendation for interleukin-6 inhibitors.

The National Institutes of Health COVID-19 Treatment Guidelines Panel Provides Recommendations for Dexamethasone in Patients with COVID-19

(Last updated June 25, 2020)

Introduction

Patients with severe COVID-19 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 harmful effects. Small, retrospective cohort studies and case series have yielded conflicting results; both beneficial[1-4] and harmful[5,6] effects have been reported in studies that have evaluated short courses of corticosteroids in patients with COVID-19.

A preliminary, unpublished analysis from a large, multicenter, randomized, open-label trial for hospitalized patients in the United Kingdom showed that patients who were randomized to receive dexamethasone had a reduced rate of mortality compared to those who received standard of care.[7] This benefit was observed in patients with severe COVID-19 (defined as those who required supplemental oxygen) and was greatest in those who required mechanical ventilation at enrollment. No benefit of dexamethasone was observed in patients who did not require supplemental oxygen at enrollment.

Based on these preliminary results:

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using dexamethasone (at a dose of 6 mg per day for up to 10 days) in patients with COVID-19 who are mechanically ventilated **(AI)** and in patients with COVID-19 who require supplemental oxygen but who are not mechanically ventilated **(BI)**.
- The Panel **recommends against** using dexamethasone in patients with COVID-19 who do not require supplemental oxygen **(AI)**.

Clinicians should refer to the Additional Considerations section below for further guidance before prescribing dexamethasone for a patient with COVID-19.

Clinical Trial Data That Supports the Panel's Recommendation

The Randomised Evaluation of COVID-19 Therapy (RECOVERY) study is a multicenter, open-label trial sponsored by the National Health Service in the United Kingdom. Hospitalized patients with clinically suspected or laboratory-confirmed COVID-19 were randomized to receive one of several potential treatments for COVID-19 plus standard of care or standard of care alone. In one of the study arms, dexamethasone 6 mg daily was administered either orally or intravenously for 10 days (or until hospital discharge, whichever came first). Recruitment was stopped by the steering committee of the study on June 8, 2020, when a sufficient number of participants were enrolled to assess benefit.

A preliminary analysis was performed on 6,425 participants, with 2,104 participants in the dexamethasone arm and 4,321 in the control arm. The mean age of the study population was 66.1 years, 64% of participants were male, and 56% had at least one major comorbidity. At enrollment, 16% of the participants required invasive mechanical ventilation, 60% had received supplemental oxygen but no invasive ventilation, and 24% required no oxygen supplementation. Very few participants who were included in this analysis received hydroxychloroquine, lopinavir/ritonavir, remdesivir, or tocilizumab; approximately 7% of participants in the standard of care arm received dexamethasone after randomization.

Results have been released for the primary endpoint of 28-day mortality.[7] Overall, 21.6% of participants in the dexamethasone arm and 24.6% of those in the control arm died within 28 days of study enrollment (age-adjusted rate ratio [RR] 0.83; 95% confidence interval [CI], 0.74–0.92, $P < 0.001$). There was evidence of a significant interaction between baseline severity of COVID-19 and the effect of dexamethasone. The survival benefit was greatest among dexamethasone-treated participants who required invasive mechanical ventilation at randomization: 29.0% of these participants died within 28 days of study enrollment compared with 40.7% in the control arm (RR 0.65; 95% CI, 0.51–0.82, $P < 0.001$). Additionally, 21.5% of dexamethasone-treated patients who required supplemental oxygen at enrollment died within 28 days of enrollment compared with 25.0% in the control arm (RR 0.80; 95% CI, 0.70–0.92, $P = 0.002$). However, no survival benefit was observed among the participants who did not require oxygen therapy at enrollment (RR 1.22; 95% CI, 0.93–1.61, $P = 0.14$).[8]

It should be noted that the age distribution of participants differed by respiratory support status at the time of randomization. The participants who received mechanical ventilation were more likely to be aged <70 years. Among the participants who were aged >80 years, only 1% were mechanically ventilated, while 62% and 37% were in the oxygen group and no oxygen group, respectively. Therefore, the survival benefit of dexamethasone for mechanically ventilated patients aged >80 years is unknown.

Full analysis of this study is ongoing. At this time, the results of other key study endpoints, the potential adverse events, and the efficacy of dexamethasone in key subgroups (e.g., age groups, patients with comorbidities, pregnant patients, children) are not yet known. In addition, the individuals with COVID-19 who required oxygen but not mechanical ventilation were a heterogeneous group, and it is unclear whether dexamethasone will be more or less beneficial for other subsets of patients (e.g., those who require high levels of supplemental oxygen).

Additional Considerations

- The results of the RECOVERY trial have not yet been published in a peer-reviewed journal.
- Remdesivir was not part of the treatment in the RECOVERY trial; therefore, the safety and efficacy of coadministering remdesivir and dexamethasone are not known.
- Very few pediatric or pregnant patients with COVID-19 were included in the RECOVERY trial; therefore, the safety and efficacy of using dexamethasone in these patients are unknown.
- It should be noted that in the RECOVERY trial, patients were not enrolled into the dexamethasone study arm (or included in the analysis) if their physicians decided that they were not suitable for corticosteroid therapy for any reason. Before initiating dexamethasone, clinicians should review the patient's medical history and assess the potential risks and benefits of administering corticosteroids to the patient.
- Clinicians should closely monitor patients with COVID-19 who are receiving dexamethasone for adverse effects (e.g., hyperglycemia, secondary infections).
- Using systemic corticosteroids may increase the risk of reactivation of latent infections (e.g., hepatitis B virus, herpesviruses, strongyloidiasis, tuberculosis).
- Dexamethasone is a moderate cytochrome P450 (CYP) 3A4 inducer, which may reduce the concentration and potential efficacy of concomitant medications that are CYP3A4 substrates. Clinicians should review a patient's medication regimens to assess potential interactions.
- At this time, it is not known whether other corticosteroids, such as prednisone, methylprednisolone, or hydrocortisone, will have a similar benefit to dexamethasone. Of note, the dose equivalencies for dexamethasone 6 mg daily are prednisone 38 mg, methylprednisolone 32 mg, and hydrocortisone 160 mg.

- 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.[9,10]

Summary

Based on the preliminary, unpublished results of the RECOVERY trial, the Panel recommends dexamethasone 6 mg daily for up to 10 days in patients with COVID-19 who are on mechanical ventilation **(AI)** or those who require supplemental oxygen but who are not on mechanical ventilation **(BI)**. The Panel **recommends against** using dexamethasone to treat patients with COVID-19 who do not require supplemental oxygen **(AI)**. The Panel may modify these recommendations based on the final published results of this study and the results of other ongoing studies.

Recommendation Rating Scheme

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

Rating of Evidence: *I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion*

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Introduction

(Last updated May 12, 2020)

These Treatment Guidelines have been developed to inform clinicians 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 becomes available.

The recommendations in these Guidelines are based on scientific evidence and expert opinion. Each recommendation includes two ratings: a letter (**A**, **B**, or **C**) that indicates the strength of the recommendation and a Roman numeral (**I**, **II**, or **III**) that indicates the quality of the evidence that supports the recommendation (see Table 1).

Panel Composition

Members of the COVID-19 Treatment Guidelines Panel (the Panel) were appointed by the Panel co-chairs and chosen 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 College of Chest Physicians
- American College of Emergency Physicians
- 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 this document.

The names, affiliations, and conflict of interest disclosures of the Panel members, ex-officio members, and support staff are provided in the Panel Roster and Financial Disclosures.

Development of the Guidelines

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

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

Each Guideline section has been reviewed, modified as necessary, and voted on by the entire Panel. A majority vote was required for a recommendation to be included in the posted Guidelines. 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 include, but are not limited to, the type of study (e.g., case series, prospective cohort, randomized controlled trial), the quality and suitability of the methods, the number of participants, and the effect sizes observed. Each recommendation is assigned two ratings according to the scheme presented in 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 with clinical outcomes and/or validated laboratory endpoints
B: Moderate recommendation for the statement	**II:** One or more well-designed, nonrandomized trials or observational cohort studies
C: Optional recommendation for the statement	**III:** Expert opinion

It is important to note that at present, to develop the recommendations in these Guidelines, the Panel relied heavily on experience with other diseases, supplemented with evolving personal clinical experience with COVID-19, and incorporated the rapidly growing published scientific literature on COVID-19. When information existed in other published guidelines that the Panel felt important to include in these Guidelines, the information was included with permission from the original sources.

Evolving Knowledge on Treatment for COVID-19

Currently there are no Food and Drug Administration (FDA)-approved drugs for COVID-19. However, an array of drugs approved for other indications, as well as multiple investigational agents, are being studied for the treatment of COVID-19 in several hundred clinical trials around the globe. These trials can be accessed at *ClinicalTrials.gov*. In addition, providers can access and prescribe investigational drugs or agents approved or licensed for other indications through various mechanisms, including Emergency Use Authorizations (EUA), Emergency Investigational New Drug (EIND) applications, compassionate use or expanded access programs with drug manufacturers, and/or off-label use.

For this reason, whenever possible, the Panel recommends that promising, unapproved or unlicensed treatments for COVID-19 be studied in well-designed controlled clinical trials. This includes drugs that have been approved or licensed for other indications. 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 such trials are still seeking guidance about whether to use these agents.

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 together with their provider.

Overview and Spectrum of COVID-19

(Last updated June 11, 2020)

Epidemiology

The COVID-19 pandemic has exploded since cases were first reported in China in December 2019. As of June 4, 2020, more than 6.5 million cases of COVID-19—caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection—have been reported globally, including >380,000 deaths. Cases have been reported in more than 180 countries, including all 50 states of the United States.[1,2]

Individuals of all ages are at risk for infection and severe disease. However, the probability of fatal disease is highest in people aged ≥65 years and those living in a nursing home or long-term care facility.

Others at highest risk for COVID-19 are people of any age with certain underlying conditions, especially when not well-controlled, including:[3-7]

- Hypertension
- Cardiovascular disease
- Diabetes
- Chronic respiratory disease
- Cancer
- Renal disease, *and*
- Obesity.

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.[4,8,9] The spectrum of illness can range from asymptomatic infection to severe pneumonia with acute respiratory distress syndrome (ARDS) and death. In a summary of 72,314 persons with COVID-19 in China, 81% of cases were reported to be mild, 14% were severe, and 5% were critical.[10] In a report of 1,482 hospitalized patients with confirmed COVID-19 in the United States, the most common presenting symptoms were cough (86%), fever or chills (85%), and shortness of breath (80%), diarrhea (27%), and nausea (24%).[7] Other reported symptoms have included, but are not limited to, sputum production, headache, dizziness, rhinorrhea, anosmia, dysgeusia, sore throat, abdominal pain, anorexia, and vomiting.

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

Abnormalities in chest X-ray vary, but typically reveal bilateral multi-focal opacities. Abnormalities seen in computed tomography (CT) of the chest also vary, but typically reveal bilateral peripheral ground-glass opacities with the development of areas of consolidation later in the clinical course.[11] Imaging may be normal early in infection and can be abnormal in the absence of symptoms.[11]

Routes of SARS-CoV-2 Transmission and Standard Means of Prevention

The onset and duration of viral shedding and period of infectiousness are not completely defined. Asymptomatic or pre-symptomatic individuals infected with SARS-CoV-2 may have viral RNA detected

in upper respiratory specimens before the onset of symptoms.[12] Transmission of SARS-CoV-2 from asymptomatic individuals has been described.[13-15] The extent to which this occurs remains unknown.

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Testing for SARS-CoV-2 Infection

(Last updated June 11, 2020)

Summary Recommendations
• The COVID-19 Treatment Guidelines Panel (the Panel) recommends that a molecular or antigen test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) should be used to diagnose acute SARS-CoV-2 infection **(AIII)**. • The Panel **recommends against** the use of serologic testing as the sole basis for diagnosis of acute SARS-CoV-2 infection **(AIII)**. • The Panel **recommends against** the use of serologic 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 with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion

Virologic Testing for SARS-CoV-2 Infection

Virologic testing (i.e., using a molecular diagnostic or antigen test to detect SARS-CoV-2) should be done in all persons with a syndrome consistent with COVID-19 and in people with known high-risk exposures to SARS-CoV-2. Ideally, virologic testing should also be performed in people likely to be at repeated risk of exposure, such as health care workers and first responders. For more information, see the Centers for Disease Control and Prevention (CDC) COVID-19 website.

While initial diagnostic tests for SARS-CoV-2 infection have relied on reverse transcriptase polymerase chain reaction platforms, more recent tests have included a variety of additional platforms. A number of diagnostic tests for SARS-CoV-2 infection have received emergency use authorizations (EUAs) issued by the Food and Drug Administration (FDA).[1] Formal comparisons of the sensitivity and specificity of these tests are in progress.

The CDC recommends that nasopharynx samples be used to detect SARS-CoV-2. Nasal swabs or oropharyngeal swabs are acceptable alternatives.[2] Although lower respiratory tract samples have a higher yield than upper tract samples, they are often not obtained because of concerns about aerosolization of virus during sample collection procedures.

The CDC has established a priority system for diagnostic testing for SARS-CoV-2 infection based on the availability of tests;[3] the CDC testing guidance is updated periodically.

The following are the current CDC priorities for COVID-19 diagnostic testing:

High Priority:

- Hospitalized patients **with symptoms**
- Health care facility workers, workers in congregate living settings, and first responders **with symptoms**
- Residents in long-term care facilities or other congregate living settings, including prisons and shelters, **with symptoms**.

Priority:

- Persons **with symptoms** of potential COVID-19 infection, including fever, cough, shortness of breath, chills, muscle pain, new loss of taste or smell, vomiting or diarrhea, and/or sore throat
- Persons **without symptoms** who are prioritized by health departments or clinicians, for any reason, including but not limited to public health monitoring, sentinel surveillance, or screening of

other asymptomatic individuals according to state and local plans

Molecular diagnostic and antigen tests can yield false-negative results. In people with a high likelihood of infection based on exposure history and/or clinical presentation, a single negative test result does not completely exclude SARS-CoV-2 infection, and repeat testing should be considered. When a person who is strongly suspected to have SARS-CoV-2 infection has a negative result on an initial antigen test, repeat testing using a molecular diagnostic test may be warranted.

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

Unlike molecular diagnostic and antigen tests for SARS-CoV-2 that detect the presence of the virus, serologic tests are intended to identify persons with recent or prior SARS-CoV-2 infection. Because it may take 21 days or longer after symptom onset for seroconversion or detection of immunoglobulin M and/or immunoglobulin G antibodies to SARS-CoV-2,[4-9] the Panel does not recommend the use of serologic testing as the sole basis for diagnosing acute SARS-CoV-2 infection **(AIII)**. Given that molecular diagnostic tests and antigen tests for SARS-CoV-2 occasionally yield false-negative results, in some settings, serologic tests have been used as an additional diagnostic test in patients strongly suspected to have SARS-CoV-2 infection.

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

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

- Important performance characteristics, including the sensitivity and specificity (i.e., the rate of true positive and true negative results) of many of the commercially available serologic tests, have not been fully characterized. Serologic assays that have FDA EUAs are preferred for public health and clinical use. Formal comparisons of serologic tests are in progress.
- 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 serologic tests are performed and antibody is detected, results should be interpreted with caution for the following reasons:

- It is currently unknown how long antibodies persist following infection, *and*
- It is currently unknown whether the presence of antibody confers protective immunity against future infection.

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

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

- Determine who may be eligible to donate blood to manufacture convalescent plasma.
- Measure the immune response in SARS-CoV-2 vaccine studies.
- Estimate the proportion of the population exposed to SARS-CoV-2.

Lastly, serologic tests **should not be used** to:

- Make decisions about the grouping of persons residing in or being admitted to congregate settings (e.g., schools, dormitories, correctional facilities), *or*
- Determine whether persons should return to the workplace.

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Persons at Risk for Infection with SARS-CoV-2

(Last updated April 21, 2020)

Pre-Exposure Prophylaxis

The COVID-19 Treatment Guidelines Panel (the Panel) **does not recommend** the use of any agents for SARS-CoV-2 pre-exposure prophylaxis (PrEP) outside the setting of a clinical trial **(AIII)**.

At present, no agent given before an exposure (i.e., as PrEP) is known to be effective in preventing SARS-CoV-2 infection. Clinical trials using hydroxychloroquine, chloroquine, or HIV protease inhibitors as PrEP are in development or underway.

Post-Exposure Prophylaxis

The Panel **does not recommend** the use of any agents for SARS-CoV-2 post-exposure prophylaxis (PEP) outside the setting of a clinical trial **(AIII)**.

At present, no agent is known to be effective for preventing SARS-CoV-2 infection after an exposure (i.e., as PEP). Potential options for PEP currently under investigation in clinical trials include hydroxychloroquine, chloroquine, or lopinavir/ritonavir.

Management of Persons with COVID-19

(Last updated June 11, 2020)

Patients with severe acute respiratory syndrome coronavirus 2 (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 management of patients according to illness severity. Currently, the Food and Drug Administration has not approved any drugs for the treatment of COVID-19. However, an array of drugs approved for other indications, as well as multiple investigational agents, are being studied for the treatment of COVID-19 in several hundred clinical trials around the globe. Some drugs can be accessed through Emergency Use Authorization, expanded access programs, or compassionate use mechanisms. Available clinical data for these drugs under investigation are discussed in Antiviral Therapy and Immune-Based Therapy.

In general, adults with COVID-19 can be grouped into the following severity of illness categories, although the criteria in each category may overlap or vary across guidelines and clinical trials:

- *Asymptomatic or Presymptomatic Infection:* Individuals who test positive for SARS-CoV-2 by virologic testing using a molecular diagnostic (e.g., polymerase chain reaction) or antigen test, but have no symptoms.
- *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) without shortness of breath, dyspnea, or abnormal chest imaging.
- *Moderate Illness:* Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO_2) ≥94% on room air at sea level.
- *Severe Illness:* Individuals who have respiratory frequency >30 breaths per minute, SpO_2 <94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mmHg, or lung infiltrates >50%.
- *Critical Illness:* Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

In pediatric patients, radiographic abnormalities are common and, for the most part, should not be used as the sole criteria to define COVID-19 illness category. Normal values for respiratory rate also vary with age in children, thus hypoxia should be the primary criteria to define severe illness, especially in younger 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 at present what percentage of individuals who present with asymptomatic infection may progress to clinical disease. Some asymptomatic individuals have been reported to have objective radiographic findings consistent with COVID-19 pneumonia. Over time, 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 infections.[1]

Persons who test positive for SARS-CoV-2 by molecular diagnostic or antigen testing (see Testing for SARS-CoV-2) and who are asymptomatic should self-isolate at home. If they remain asymptomatic, they can discontinue isolation 10 days after the date of their first positive SARS-CoV-2 test.[2] Health care workers who test SARS-CoV-2 positive and are asymptomatic may obtain additional guidance

from their occupational health service. See the Centers for Disease Control and Prevention COVID-19 website for detailed information. Individuals who become symptomatic should contact their health care provider for further guidance. Current CDC recommendations for individuals who develop symptoms are to self-isolate for at least 10 days from the onset of their symptoms and until they have no fever and improvement in respiratory symptoms for at least 3 days.

The Panel recommends no additional laboratory testing and no specific treatment for persons with suspected or confirmed asymptomatic or presymptomatic SARS-CoV-2 infection (AIII).

Mild Illness

Patients may have mild illness defined by a variety of signs and symptoms (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without 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 remote visits.

All patients with symptomatic COVID-19 and risk factors for severe disease should be closely monitored. In some patients, the clinical course may rapidly progress.[3,4]

No specific laboratory evaluations are indicated in otherwise healthy patients with mild COVID-19 disease.

There are insufficient data to recommend either for or against any antiviral or immune-based therapy in patients with COVID-19 who have mild illness.

Moderate Illness

Moderate COVID-19 illness is defined as evidence of lower respiratory disease by clinical assessment or imaging with SpO_2 ≥94% on room air at sea level. Given that pulmonary disease can rapidly progress in patients with COVID-19, close monitoring of patients with moderate disease is recommended. If bacterial pneumonia or sepsis is strongly suspected, administer empiric antibiotic treatment for community-acquired pneumonia, re-evaluate daily, and if there is no evidence of bacterial infection, de-escalate or stop antibiotics.

Hospital infection prevention and control measures include use of personal protective equipment for droplet and contact precautions along with eye protection (e.g., masks, face shields/goggles, gloves, gowns) and single-patient dedicated medical equipment (e.g., stethoscopes, blood pressure cuffs, thermometers).[5,6] The number of individuals and providers entering the room of a patient with COVID-19 should be limited. If necessary, patients with confirmed COVID-19 may be cohorted in the same room. If available, airborne infection isolation rooms (AIIRs) should be used for patients who will be undergoing any aerosol-generating procedures. During these procedures, all staff should wear fit-tested respirators (N95 respirators) or powered, air-purifying respirators (PAPRs) rather than a surgical mask.[7]

The optimal pulmonary imaging technique for people with COVID-19 is yet to be defined. Initial evaluation may include chest x-ray, ultrasound, or if indicated, computerized tomography (CT). Electrocardiogram (ECG) should be performed if indicated. Laboratory testing includes a complete blood count (CBC) with differential and a metabolic profile, including liver and renal function tests. Measurements of inflammatory markers such as C-reactive protein (CRP), D-dimer, and ferritin, while not part of standard care, may have prognostic value.

Clinicians should refer to Antiviral Therapy and Table 2a and Immune-Based Therapy and Table 3a to review the available clinical data regarding investigational drugs being evaluated for treatment of COVID-19.

Severe Illness

Patients with COVID-19 are considered to have severe illness if they have SpO_2 <94% on room air at sea level, respiratory rate >30, PaO_2/FiO_2 <300 mmHg, or lung infiltrates >50%. These patients may experience rapid clinical deterioration and will likely need to undergo aerosol-generating procedures. They should be placed in AIIRs, if available. Administer oxygen therapy immediately using nasal cannula or high-flow oxygen.

If secondary bacterial pneumonia or sepsis is suspected, administer empiric antibiotics, re-evaluate daily, and, if there is no evidence of bacterial infection, de-escalate or stop antibiotics.

Evaluation should include pulmonary imagining (chest x-ray, ultrasound, or, if indicated, CT) and ECG, if indicated. Laboratory evaluation includes a CBC with differential and a metabolic profile, including liver and renal function tests. Measurements of inflammatory markers such as CRP, D-dimer, and ferritin, while not part of standard care, may have prognostic value.

Clinicians should refer to Antiviral Therapy and Table 2a and Immune-Based Therapy and Table 3a to review the available clinical data regarding drugs being evaluated for treatment of COVID-19.

Critical Illness

For additional details, see Care of Critically Ill Patients with COVID-19.

Severe cases of COVID-19 may be associated with acute respiratory distress syndrome, septic shock that may represent virus-induced distributive shock, cardiac dysfunction, elevations in multiple inflammatory cytokines that provoke a cytokine storm, 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 AIIRs when available.

Most of the recommendations for the management of critically ill patients with COVID-19 are extrapolated from experience with other life-threatening infections.[8] 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, although special precautions to prevent environmental contamination by SARS-CoV-2 is warranted.

The Surviving Sepsis Campaign (SSC), an initiative supported by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine, issued Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19) in March 2020.[8] The Panel relied heavily on the SSC guidelines in making the recommendations in these Treatment Guidelines and gratefully acknowledges the work of the SSC COVID-19 Guidelines Panel.

As with any patient in the intensive care unit (ICU), successful clinical management of a patient with COVID-19 depends on attention to the primary process leading to the ICU admission, but also to other comorbidities and nosocomial complications.

Clinicians should refer to Antiviral Therapy and Table 2a and Immune-Based Therapy and Table 3a to review the available clinical data regarding drugs being evaluated for treatment of COVID-19.

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Special Considerations in Pregnancy and Post-Delivery

(Last updated May 12, 2020)

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 on the management of pregnant patients with COVID-19.[1-4] This section of the Treatment Guidelines complements that guidance and focuses on considerations regarding management of COVID-19 in pregnancy.

Limited information is available regarding the effect of COVID-19 on obstetric or neonatal outcomes. Initial reports of COVID-19 disease acquired in the third trimester were largely reassuring, but most data are limited to case reports and case series.[5,6] In one of the larger series from Wuhan, China, pregnant women did not appear to be at risk for more severe disease.[7] Among 147 pregnant women with COVID-19 (64 confirmed cases, 82 suspected cases, and 1 case of asymptomatic infection), 8% had severe disease and 1% had critical disease. In comparison, in the general population of persons with COVID-19, 13.8% had severe disease and 6.1% had critical disease.[8] While data are still emerging, the US experience has been similar to date.[9]

ACOG has developed algorithms to evaluate pregnant outpatients with suspected or confirmed COVID-19.[10] As with non-pregnant patients, a wide range of clinical manifestations of the disease occur, from mild symptoms that can be managed with supportive care at home to severe disease and respiratory failure requiring intensive care unit admission. As with other patients, in the pregnant patient with symptoms compatible with COVID-19, the illness severity, underlying co-morbidities, and clinical status should all be assessed to determine whether in-person evaluation for potential hospitalization is needed.

If hospitalization is indicated, ideally the care should be provided in a facility that has the capability to conduct close maternal and fetal monitoring. The principles of management of COVID-19 in the pregnant patient may include:

- Fetal and uterine contraction monitoring
- Individualized delivery planning
- A team-based approach with multispecialty consultation.

Other recommendations, as outlined for the non-pregnant patient, will also apply in pregnancy.

Timing of Delivery:

- In most cases, the timing of delivery should be dictated by obstetric indications rather than maternal diagnosis of COVID-19. For women with suspected or confirmed COVID-19 early in pregnancy who recover, no alteration to the usual timing of delivery is indicated.
- For women with suspected or confirmed COVID-19 in the third trimester, it is reasonable to attempt to postpone delivery (if no other medical indications arise) until a negative test result is obtained or quarantine restrictions are lifted in an attempt to avoid virus transmission to the neonate.
- In general, a diagnosis of COVID-19 in pregnancy is not an indication for early delivery.[11]
- Based on limited data on primarily cesarean deliveries, there appears to be no clear evidence of vertical transmission of SARS-CoV-2 via the transplacental route, but this has not been definitively ruled out.[11]

Management of COVID-19 in the Setting of Pregnancy:

- There are no Food and Drug Administration-approved medications for the treatment of COVID-19.
- Most clinical trials to date have excluded pregnant and lactating women.
- Decisions regarding the use of drugs approved for other indications or investigational agents to treat COVID-19 must be made with shared decision-making, considering the safety of the medication and the risk and seriousness of maternal disease (see Antiviral Therapy, Immune-Based Therapy and Considerations for Certain Concomitant Medications in Patients with COVID-19).
- Involvement of a multidisciplinary team in these discussions, including, among others, specialists in obstetrics, maternal-fetal medicine, and pediatrics, is recommended.
- Enrollment of pregnant and lactating women in clinical trials (if eligible) is encouraged.

Post-Delivery:

- Currently the CDC recommends that the determination of whether or not to separate a mother with known or suspected COVID-19 and her infant should be made on a case-by-case basis using shared decision-making between the mother and the clinical team.
- ACOG supports breastfeeding for infants. They recommend that, for women who are PUI or confirmed to have SARS-CoV-2 infection, the decision about whether and how to start or continue breastfeeding be made by the mother in coordination with her family and health care practitioners.[11]
- CDC has developed interim guidance on breastfeeding, recommending that women who intend to breastfeed and who are temporarily separated from their infants express their breastmilk, ideally from a dedicated pump, practice good hand hygiene before and after pumping, and consider having a healthy person feed the infant.
- CDC advises that women with COVID-19 who choose to room-in with their infants and feed them at the breast should practice good hand hygiene and wear a facemask to prevent transmission of the virus to the infant via respiratory droplets during breastfeeding.[1] SARS-CoV-2 has not been isolated from breast milk.[5]

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Special Considerations in Children

(Last updated June 11, 2020)

Data on disease severity and pathogenesis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children are limited. Overall, several large epidemiologic studies suggest that acute disease manifestations are substantially less severe in children than in adults, although there are reports of children with COVID-19 requiring intensive care unit (ICU)-level care.[1-11] Recently, SARS-CoV-2 has been associated with a potentially severe inflammatory syndrome in children (multisystem inflammatory syndrome in children [MIS-C], which is discussed below). Preliminary data from the Centers for Disease Control and Prevention (CDC) also show that hospitalization rates and ICU admission rates for children are lower than for adults. Severe cases of COVID-19 in children were associated with younger age and underlying conditions, although a significant number of the pediatric cases did not have complete data available at the time of the preliminary report. Without widespread testing, including for mild symptoms, the true incidence of severe disease in children is unclear. Data on perinatal vertical transmission to neonates are limited to small case series with conflicting results; some studies have demonstrated lack of transmission, whereas others have not been able to definitively rule out this possibility.[12-14] 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 the CDC.

Insufficient data are available to clearly establish risk factors for severe COVID-19 disease in children. Based on adult data and extrapolation from other pediatric respiratory viruses, severely immunocompromised children and those with underlying cardiopulmonary disease may be at higher risk for severe disease. Children with risk factors recognized in adults, including obesity, diabetes, and hypertension, may also be at risk, although there are no published data supporting this association and insufficient data to guide therapy. Guidance endorsed by the Pediatric Infectious Diseases Society has recently been published, which provides additional specific risk categorization when considering therapy.[15] As data emerge on risk factors for severe disease, it may be possible to provide more directed guidance for specific populations at high risk for COVID-19 and to tailor treatment recommendations accordingly.

Currently, there are no Food and Drug Administration (FDA)-approved agents for the treatment of COVID-19. Based on preliminary clinical trial data, the investigational antiviral agent remdesivir is recommended for the treatment of COVID-19 in hospitalized patients with severe disease (see Remdesivir for detailed information). Of note, remdesivir has not been evaluated in clinical trials that include children with COVID-19. Remdesivir is available for children through an FDA Emergency Use Authorization or through a compassionate use program.

For other agents outlined in these guidelines, there are insufficient data to recommend for or against the use of specific antivirals or immunomodulatory agents for the treatment of COVID-19 in pediatric patients. General considerations such as underlying conditions, disease severity, and potential for drug toxicity or drug interactions may inform management decisions on a case-by-case basis. Enrollment of children in clinical trials should be prioritized when trials are available. A number of additional drugs are being investigated for the treatment of COVID-19 in adults; clinicians can refer to the Antiviral Therapy and Immune Based Therapy sections of these guidelines to review special considerations for use of these drugs in children and refer to Table 2b and Table 3b for dosing recommendations in children.

Multisystem Inflammatory Syndrome in Children

Emerging reports from Europe and the United States have suggested that COVID-19 may be associated with MIS-C (also referred to as pediatric multisystem inflammatory syndrome–temporally associated with SARS-CoV-2 [PMIS-TS]). The syndrome was first described in the United Kingdom, where previously healthy children with severe inflammation and Kawasaki disease-like features were identified

to have current or recent infection with SARS-CoV-2.[16,17] Additional cases of MIS-C have been reported in other European countries, including Italy and France.[18,19] Emerging data suggest that MIS-C may be associated with pediatric patients who are slightly older than children typically seen with Kawasaki disease, and some cases of MIS-C in young adults have been reported.

In the United States, from April 16 through May 4, 2020, the New York City Department of Health and Mental Hygiene received reports of 15 hospitalized children with clinical presentation consistent with MIS-C. Subsequently, the New York State Department of Health has been investigating several hundred cases and a few deaths in children with similar presentations, many of whom tested positive for SARS-CoV-2 infection by reverse transcriptase polymerase chain reaction (PCR) or serology.[20] Several other states are now reporting cases consistent with MIS-C.

The current case definition for MIS-C can be found on the CDC website. This case definition, which may evolve as more data become available, includes:

- Fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multiorgan involvement, *and*
- No alternate diagnosis, *and*
- Recent or current SARS-CoV-2 infection or exposure to COVID-19.

From the available data, patients with MIS-C present with persistent fever, evidence of systemic inflammation, and a variety of signs and symptoms of multiorgan system involvement, including cardiac, gastrointestinal, renal, hematologic, dermatologic, and neurologic involvement.

Some patients who meet criteria for MIS-C also meet criteria for complete or incomplete Kawasaki disease. An observational study compared data from Italian children with Kawasaki-like illness that was diagnosed before and after the onset of the SARS-CoV-2 epidemic. The data suggest that the SARS-CoV-2-associated cases occurred in children who were older than the children with Kawasaki-like illness diagnosed prior to the COVID-19 epidemic. In addition, the rates of cardiac involvement, associated shock, macrophage activation syndrome, and need for adjunctive steroid treatment were higher for the SARS-CoV-2-associated cases.[18] Many patients with MIS-C have abnormal markers of cardiac injury or dysfunction, including troponin and brain natriuretic protein. Echocardiographic findings include impaired left ventricular function, as well as coronary artery dilations, and rarely, coronary artery aneurysms. At presentation, few patients are SARS-CoV-2 PCR positive (nasopharyngeal or nasal swab or stool sample), but most have detectable antibodies to SARS-CoV-2. Emerging observations suggest that there may be a wider range of severity of symptoms than initially recognized. Epidemiologic and clinical data suggest that MIS-C may represent a post-infectious inflammatory phenomenon rather than a direct viral process. The role of asymptomatic infection and the pattern of timing between SARS-CoV-2 infection and MIS-C are not well understood, and currently a causal relationship is not established.

Currently, there is limited information available about risk factors, pathogenesis, clinical course, and treatment for MIS-C. Supportive care remains the mainstay of therapy. There are currently insufficient data for the COVID-19 Treatment Guidelines Panel to recommend either for or against any therapeutic strategy for the management of MIS-C. Although no definitive data are available, many centers consider the use of intravenous immune globulin, steroids, and other immunomodulators (including interleukin-1 and interleukin-6 inhibitors) for therapy, and antiplatelet and anticoagulant therapy. The role of antiviral medications that specifically target SARS-CoV-2 is not clear at this time. MIS-C management decisions should involve a multidisciplinary team of pediatric specialists in intensive care, infectious diseases, cardiology, hematology, and rheumatology.

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Care of Critically Ill Patients with COVID-19

(Last updated June 25, 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 fit-tested respirators (N95 respirators) or powered air-purifying respirators, rather than surgical masks, in addition to other personal protective equipment (i.e., gloves, gown, and eye protection such as a face shield or safety goggles) **(AIII)**.
- The Panel recommends that endotracheal intubation for patients with COVID-19 be performed by health care providers with extensive airway management experience, if possible **(AIII)**.
- The Panel recommends that intubation be achieved by video laryngoscopy, if possible **(CIII)**.

Hemodynamic Support:

- The Panel recommends norepinephrine as the first-choice vasopressor **(AII)**.
- For adults with COVID-19 and refractory shock, the Panel recommends using low-dose corticosteroid therapy ("shock-reversal") over no corticosteroid **(BII)**.

Ventilatory Support:

- 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) **(BI)**.
- 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 for whom HFNC is not available **(BIII)**.
- For adults with COVID-19 who are receiving supplemental oxygen, the Panel recommends close monitoring for worsening respiratory status and that intubation, if it becomes necessary, be performed by an experienced practitioner in a controlled setting **(AII)**.
- 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 **(CIII)**.
- The Panel **recommends against** using awake prone positioning as a rescue therapy for refractory hypoxemia to avoid intubation in patients who otherwise require intubation and mechanical ventilation **(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 tidal volumes (VT >8 mL/kg) **(AI)**.
- 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 **(BII)**.
- For mechanically ventilated adults with COVID-19, severe ARDS, and hypoxemia despite optimized ventilation and other rescue strategies, 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)**.
- There are insufficient data to recommend either for or against the routine use of extracorporeal membrane oxygenation (ECMO) for patients with COVID-19 and refractory hypoxemia.

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:

- The Panel recommends the investigational antiviral agent **remdesivir** for treatment of COVID-19 in hospitalized patients with SpO_2 ≤94% on room air (at sea level) or those who require supplemental oxygen **(AI)**.

- The Panel recommends **remdesivir** for treatment of COVID-19 in patients who are on mechanical ventilation or ECMO **(BI)**.
- The Panel recommends using dexamethasone (at a dose of 6 mg per day for up to 10 days) in patients with COVID-19 who are mechanically ventilated **(AI)** and in patients with COVID-19 who require supplemental oxygen but who are not mechanically ventilated **(BI)**.
- The Panel **recommends against** using dexamethasone in patients with COVID-19 who do not require supplemental oxygen **(AI)**.
- There are insufficient data for the Panel to recommend either for or against any other immunomodulatory therapy in patients with severe COVID-19 disease.
- 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.

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

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion

General Considerations

(Last updated April 21, 2020)

Co-Morbid Conditions

The vast majority of patients who are critically ill with COVID-19 have attributes and co-morbidities that place them at higher risk for serious disease, such as older age, hypertension, cardiovascular disease, diabetes, chronic respiratory disease, cancer, renal disease, and obesity.[1]

As with any patient in the intensive care unit (ICU), successful management depends on attention to the primary process leading to ICU admission, as well as to other co-morbidities and nosocomial complications.

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.[2-7] There is appropriate concern about performing pulmonary diagnostic procedures, such as bronchoscopy or other airway sampling that requires disruption of a closed airway circuit. Thus, while some clinicians do not routinely start empiric broad-spectrum antimicrobial therapy for COVID-19 patients with severe disease, other experienced clinicians routinely use such therapy. For the treatment of shock, however, broad-spectrum empiric antimicrobial therapy is standard of care. Antibiotic stewardship is critical to avoid reflexive or continued courses of antibiotics.

Septic Shock and Cytokine Storm Due to COVID-19

Patients with COVID-19 may express high levels of an array of inflammatory cytokines, often in the setting of deteriorating hemodynamic or respiratory status. This is often referred to as "cytokine release syndrome" or "cytokine storm," although these are imprecise terms. Intensivists need to consider the full differential diagnosis of shock to exclude other treatable causes of shock (e.g., bacterial sepsis due to pneumonia or an extra-pulmonary source, hypovolemic shock due to a gastrointestinal hemorrhage that is unrelated to COVID-19, cardiac dysfunction related to COVID-19 or comorbid atherosclerotic disease, stress-related adrenal insufficiency).

COVID-19-Induced Cardiac Dysfunction, Including Myocarditis

There is a growing body of literature relating COVID-19 to myocarditis and pericardial dysfunction in approximately 20% of patients.[3,5,8-11] Acute cardiac injury and arrhythmias have also been described in patients with COVID-19.

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 disease.[3] Continuous renal replacement therapy was needed in more than 15% of cases of critical disease in one series.[5]

Drug-Drug Interactions Between Drugs Used to Treat COVID-19 and Drugs Used to Treat Co-Morbidities

All ICU patients should routinely be monitored for drug-drug interactions. The potential for drug-drug

interactions between investigational or off-label medications used to treat COVID-19 and concurrent drugs should be considered. QTc prolongation due to agents such as chloroquine or hydroxychloroquine is a potential problem for patients with underlying heart disease and/or those who concurrently use drugs that prolong the QTc interval (e.g., azithromycin, quinolones).

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. The focus on COVID-19 should not reduce attention to minimizing conventional ICU complications in order to optimize the likelihood of a successful ICU outcome.

Goals of Care

For any critically ill patient, the goals of care must be assessed when the patient is admitted and regularly thereafter. This is essential regardless of the availability of resources, the age of the patient, or the patient's co-morbid conditions.[12,13]

The Surviving Sepsis Campaign (SSC), an initiative supported by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine, issued *Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19)* in March 2020.[14] The COVID-19 Treatment Guidelines Panel (the Panel) has based these recommendations on the SSC COVID-19 Guidelines, with permission, and the Panel gratefully acknowledges the work of the SSC COVID-19 Guidelines Panel. The Panel also acknowledges the contributions and expertise of Andrew Rhodes, MBBS, MD, of St. George's University Hospitals in London, England, and Waleed Alhazzani, MBBS, MSc, of McMaster University in Hamilton, Canada.

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Infection Control

(Last updated May 12, 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 fit-tested respirators (N95 respirators) or powered air-purifying respirators 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; bronchoscopy; open suctioning; high-flow nasal cannula (HFNC) or face mask; nebulizer treatment; manual ventilation; physical proning of the patient; disconnecting a patient from a ventilator; mini-bronchoalveolar lavage; noninvasive positive pressure ventilation (NIPPV); tracheostomy; or cardiopulmonary resuscitation.

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, staff must be fit-tested for the type used. Surgical masks block large particles, droplets, and sprays, but are less effective in blocking small particles (<5 μm) and aerosols.[3]

Recommendation:

- The Panel recommends minimizing the use of aerosol-generating procedures on COVID-19 intensive care unit patients and carrying out any necessary aerosol-generating procedures in a negative-pressure room, also known as an airborne infection isolation room (AIIR) **(AIII)**.

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 HFNC or noninvasive ventilation. HEPA filters reduce virus transmission in simulations.[4]

Recommendations:

- For health care workers who are providing usual care for non-ventilated COVID-19 patients, the Panel recommends using surgical masks or fit-tested respirators (N95 respirators), in addition to other PPE (i.e., gloves, gown, and eye protection, such as a face shield or safety goggles) **(AII)**.
- 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 surgical masks or fit-tested respirators (N95 respirators), in addition to other PPE (i.e., gloves, gown, and eye protection, such as a face shield or safety goggles) **(AII)**.

Rationale

There is evidence from viral diseases including SARS that both surgical masks and N95 masks reduce

transmission of infection.[5] 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).[6,7] The Surviving Sepsis Campaign COVID-19 Guidelines updated a recent systematic review and meta-analysis of randomized controlled trials that demonstrated no statistical difference in protection between surgical masks and N95 respirators in this setting.[8]

Recommendations:

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

Rationale

Factors that maximize the chances of first-pass success and minimize aerosolization should be used when intubating patients with suspected or confirmed COVID-19.[9,10] Thus, the Panel recommends that the health care operator 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. Finally, it is important to avoid having unnecessary staff in the room.

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Laboratory Diagnosis

(Last updated April 21, 2020)

Recommendations:

- For intubated and mechanically ventilated adults who are suspected to have COVID-19 but who do not have a confirmed diagnosis:
  - The COVID-19 Treatment Guidelines Panel (the Panel) recommends obtaining lower respiratory tract samples to establish a diagnosis of COVID-19 over upper respiratory tract (nasopharyngeal or oropharyngeal) samples **(BII)**.
  - The Panel recommends obtaining endotracheal aspirates over bronchial wash or bronchoalveolar lavage (BAL) samples when obtaining lower respiratory samples to establish a diagnosis of COVID-19 **(BII)**.

Rationale

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) poses several diagnostic challenges, including potentially discordant shedding of virus from the upper versus lower respiratory tract. COVID-19 diagnosis is currently based on using a reverse transcriptase polymerase chain reaction (RT-PCR) assay to detect viral RNA in respiratory samples. The high specificity of RT-PCR removes the need for lower respiratory tract samples to diagnose COVID-19 when a nasopharyngeal swab is positive for a patient with recent onset of the disease. Lower respiratory tract specimens are considered by some experts to have higher yield, due to high viral load, consistent with what has been observed for severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).[1-7] Thus, lower respiratory tract samples should be obtained whenever possible if there is diagnostic uncertainty regarding COVID-19.

However, BAL and sputum induction are aerosol-generating procedures and should be performed only with careful consideration of the risk to staff of aerosol generation. Endotracheal aspirates appear to carry a lower risk of aerosolization than BAL and are thought by some experts to have comparable sensitivity and specificity to BAL specimens.

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Hemodynamics

(Last updated May 12, 2020)

For the most part, these hemodynamic recommendations are similar to those previously published in the *Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016*. Ultimately, COVID-19 patients who require fluid resuscitation or hemodynamic management of shock should be treated and managed identically to those 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 over static parameters to assess fluid responsiveness **(BII)**.

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% confidence interval [CI], 0.42–0.83), intensive care unit (ICU) length of stay (mean duration -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 ($ScVO_2$)-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 **(BII)**.

Rationale

A pragmatic randomized trial that compared balanced and unbalanced crystalloids in 15,802 critically ill adults found a lower rate of a composite outcome, including death, new renal-replacement therapy, or persistent renal dysfunction (odds ratio [OR] 0.90; 95% CI, 0.82–0.99; $P = 0.04$).[5] The subset of sepsis patients in this trial (n = 1,641) was found to have a lower mortality (adjusted odds ratio 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 compared balanced crystalloids to 0.9% saline for resuscitation of critically ill adults and children 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 **(BI)**.

Rationale

A meta-analysis of 20 non-COVID-19 randomized controlled trials (n = 13,047) that compared the use of albumin or fresh-frozen plasma to crystalloids in critically ill patients found no difference in all-cause mortality,[8] while 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 suggests avoiding the use of albumin for initial, routine 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 **(AI)**.
- The Panel recommends norepinephrine as the first-choice vasopressor **(AII)**. The Panel recommends adding either vasopressin (up to 0.03 U/min) **(BII)** or epinephrine **(CII)** to norepinephrine to raise mean arterial pressure to target, or adding vasopressin (up to 0.03 U/min) **(CII)** to decrease norepinephrine dosage.
- When norepinephrine is available, the Panel **recommends against** using dopamine for patients with COVID-19 and shock **(AI)**.
- The Panel **recommends against** using low-dose dopamine for renal protection **(BII)**.
- 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 **(BII)**.
- 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 shock, the Panel recommends using low-dose corticosteroid therapy ("shock-reversal") over no corticosteroid **(BII)**.
    - A typical corticosteroid regimen in septic shock is intravenous hydrocortisone 200 mg per day administered either as an infusion or intermittent doses. The duration of hydrocortisone therapy is usually a clinical decision.

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Oxygenation and Ventilation

(Last updated June 11, 2020)

For hypoxemic patients, the recommendations below emphasize well-described and documented recommendations from the Surviving Sepsis Campaign Guidelines for adult sepsis, pediatric sepsis, and COVID-19, which provide more details about management and the data that support the recommendations.

Recommendations

- For adults with COVID-19 who are receiving supplemental oxygen, the COVID-19 Treatment Guidelines Panel (the Panel) recommends close monitoring for worsening respiratory status and that intubation, if it becomes necessary, be performed by an experienced practitioner in a controlled setting **(AII)**.
- 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) **(BI)**.
- 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 for whom HFNC is not available **(BIII)**.
- 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 **(CIII)**.
- The Panel **recommends against** using awake prone positioning as a rescue therapy for refractory hypoxemia to avoid intubation in patients who otherwise require intubation and mechanical ventilation **(AIII)**.

Rationale

Hypoxemia is common in hospitalized patients with COVID-19. The criteria for hospital admission, intensive care unit (ICU) admission, and mechanical ventilation differ between countries. In some hospitals in the United States, >25% of hospitalized patients require ICU care, mostly due to acute respiratory failure.[1-5]

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 include HFNC, NIPPV, or intubation and invasive mechanical ventilation.

HFNC and NIPPV are preferable to conventional oxygen therapy based on data from non-COVID-19 clinical trials and meta-analyses that showed reductions in the need for therapeutic escalation and the need for intubation in patients who received HFNC or NIPPV.[6,7]

HFNC is preferred over NIPPV in patients with acute hypoxemic respiratory failure based on data from an unblinded clinical trial that was performed prior to the COVID-19 pandemic. This trial found more ventilator-free days with HFNC than with conventional oxygen therapy or NIPPV (24 days vs. 22 days vs. 19 days, respectively; $P = 0.02$) and lower 90-day mortality with HFNC than with both conventional oxygen therapy (hazard ratio [HR] 2.01; 95% confidence interval [CI], 1.01–3.99) and NIPPV (HR 2.50; 95% CI, 1.31–4.78).[8]

In the subgroup of more severely hypoxemic patients with PaO_2/FiO_2 ≤200, HFNC reduced the rate

of intubation compared to conventional oxygen therapy or NIPPV (HRs 2.07 and 2.57, respectively). These findings were corroborated in a meta-analysis that showed a lower likelihood of intubation (odds ratio [OR] 0.48; 95% CI, 0.31–0.73) and ICU mortality (OR 0.36; 95% CI, 0.20–0.63) with HFNC than with NIPPV.[9] In situations where the options for respiratory support are limited, reducing the need for intubation may be particularly important.

Prone positioning improves oxygenation and patient outcomes in patients with moderate-to-severe acute respiratory distress syndrome (ARDS) that requires mechanical ventilation.[10,11] Prone positioning is thought to improve oxygenation because it improves ventilation-perfusion matching and recruits collapsed alveoli in the dorsal lungs.[12] Two case series that were published prior to the COVID-19 pandemic reported improved oxygenation and low intubation rates when placing spontaneously breathing patients with hypoxemia in the prone position,[13,14] and several new case series reported similar results with awake prone positioning in patients with COVID-19 pneumonia who required supplemental oxygen.

In a case series of 50 patients with COVID-19 pneumonia who required supplemental oxygen upon presentation to a New York City emergency department (ED), awake prone positioning improved overall median oxygen saturation. However, 13 of these patients still required intubation due to respiratory failure within 24 hours of presentation to the ED.[15] Another case series from Jiangsu province used awake prone positioning as part of a treatment strategy in nonintubated patients with COVID-19 pneumonia and reported an intubation rate of less than 1%.[16] In a report of 24 patients who required either a nasal cannula or HFNC and who had a chest computerized tomography scan that was consistent with COVID-19 pneumonia, 25% of patients tolerated prone positioning for at least 3 hours and showed >20% improvement in the partial pressure of oxygen in arterial blood. No complications were reported with prone positioning.[17] Another case series of 15 patients with ARDS due to COVID-19 pneumonia who received awake prone positioning while on noninvasive ventilation reported that all patients showed improvement in their oxygen saturation during prone positioning, with 80% of patients sustaining improved oxygenation with resupination. Seven percent of patients required intubation.[18]

Appropriate candidates for awake prone positioning are those who are able to 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 hemodynamically unstable patients, patients who recently had abdominal surgery, and patients who have an unstable spine.[19] 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.[20]

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

Early intubation may be particularly appropriate when patients have additional acute organ dysfunction or chronic comorbidities, or when HFNC and NIPPV are not available. NIPPV has a high failure rate in both patients with non-COVID-19 viral pneumonia[21,22] and patients with ARDS.[23,24] NIPPV may generate aerosol spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and thus increase nosocomial transmission of the infection.[25,26] It remains unclear whether HFNC results in a lower risk of nosocomial SARS-CoV-2 transmission.

The use of supplemental oxygen in adults with COVID-19 has not been studied, but indirect evidence from other critical illnesses suggests the optimal oxygen target is an SpO_2 between 92% and 96%:

- A meta-analysis of 25 randomized controlled trials found that a liberal oxygen strategy (median SpO_2 96%) was associated with an increased risk of hospital mortality (relative risk 1.21; 95% CI, 1.03–1.43).[27]

- The LOCO2 randomized controlled trial compared a conservative oxygen strategy (target SpO_2 88% to 92%) to a liberal oxygen strategy (target SpO_2 ≥96%).[28] The trial was stopped early due to futility. Mortality was increased among those who received the conservative oxygen therapy at Day 28 (risk difference +8%; 95% CI, -5% to +21%) and Day 90 (risk difference +14%; 95% CI, +0.7% to +27%). These differences would be important if they were real, but the study was too small to definitively confirm or exclude an effect.

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 tidal volumes (VT >8 mL/kg) **(AI)**.
- The Panel recommends targeting plateau pressures of <30 cm H_2O **(AII)**.
- The Panel recommends using a conservative fluid strategy over a liberal fluid strategy **(BII)**.
- The Panel **recommends against** the routine use of inhaled nitric oxide **(AI)**.

Rationale

Currently, there is no evidence that ventilator management of patients with ARDS due to COVID-19 should differ from the management of patients with viral pneumonia due to influenza or other respiratory viruses.

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 **(BII)**.
- 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 **(BII)**.

Rationale

Proning is a recommended strategy in non-COVID-19-related ARDS for improving oxygenation and reducing the heterogeneity of lung ventilation. Proning has been used to treat patients with COVID-19, although there is currently not enough clinical experience with this strategy to draw conclusions about its effect on long-term outcomes.[29] However, even in centers that are experienced in prone ventilation, proning requires multiple staff members to safely turn the patient and prevent dislodgement of the endotracheal tube, as well as other tubes and catheters. Each staff member should wear the recommended personal protective equipment (PPE). Depending on local resources, especially when PPE may be in short supply, the risk of COVID-19 exposure during the process of proning may outweigh the benefit of proning to the patient. Prone positioning is acceptable and feasible for pregnant patients who are mechanically ventilated, and it can be performed in the left lateral decubitus position or the fully prone position.[20]

Recommendations

- The Panel recommends using, as needed, intermittent boluses of neuromuscular blocking agents (NMBA) or continuous NMBA infusion to facilitate protective lung ventilation **(BIII)**.
- In the event of persistent patient-ventilator dyssynchrony, which places the patient at risk for

ventilator lung injury, 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 more frequently for close clinical monitoring. Therefore, in some situations, the risks of COVID-19 exposure and the use of PPE for each entry may outweigh the benefit of NMBA treatment.

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 **(CII)**.
- If recruitment maneuvers are used, the Panel **recommends against** using staircase (incremental PEEP) recruitment maneuvers **(AII)**.
- 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)**.

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Acute Kidney Injury and Renal Replacement Therapy

(Last updated June 11, 2020)

Recommendations

- For critically ill patients 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. 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 June 25, 2020)

Antiviral Therapy

Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends the investigational antiviral agent **remdesivir** for treatment of COVID-19 in hospitalized patients with SpO_2 ≤94% on room air (at sea level) or those who require supplemental oxygen **(AI)**.
- The Panel recommends **remdesivir** for treatment of COVID-19 in patients who are on mechanical ventilation or extracorporeal membrane oxygenation **(BI)**.

See the Remdesivir section for a detailed discussion of these recommendations.

Immune-Based Therapy

Several immune-based therapies that are expected to modify the course of COVID-19 infection, 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., interleukin [IL]-1 or IL-6 inhibitors). Recommendations regarding immune-based therapy can be found in Immune-Based Therapy Under Evaluation for Treatment of COVID-19.

Corticosteroids

Preliminary clinical trial data from a large, randomized, open-label trial suggest that dexamethasone reduces mortality in hospitalized patients with COVID-19 who require mechanical ventilation or supplemental oxygen.[1] The recommendations for using corticosteroids in patients with COVID-19 depend on the severity of illness. Before initiating dexamethasone, clinicians should review the patient's medical history and assess the potential risks and benefits of administering corticosteroids to the patient.

Recommendations

- The Panel recommends using dexamethasone (at a dose of 6 mg per day for up to 10 days) in patients with COVID-19 who are mechanically ventilated **(AI)** and in patients with COVID-19 who require supplemental oxygen but who are not mechanically ventilated **(BI)**.
- The Panel **recommends against** using dexamethasone in patients with COVID-19 who do not require supplemental oxygen **(AI)**.

Rationale

See the Panel's guidance on the use of dexamethasone for a detailed discussion of these recommendations.

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 **(BIII)**.
- 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 co-pathogens with COVID-19 at this time.

For patients with COVID-19, some experts routinely administer broad-spectrum antibiotics to all patients with 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 and cultures or testing of respiratory specimens are 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.

With influenza, empiric antibacterial treatment is strongly recommended for patients with initial severe disease (i.e., those with extensive pneumonia, respiratory failure, hypotension, and fever) and those who deteriorate after initial improvement.[2] These recommendations are based on observations that bacterial superinfections, especially those due to *Staphylococcus aureus* and *Streptococcus* pneumonia, are not uncommon and have dire consequences if not treated promptly.

Whether moderate or severe COVID-19 disease should be approached like severe influenza will remain uncertain until more microbiologic and clinical data become available.

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Extracorporeal Membrane Oxygenation

(Last updated April 21, 2020)

Recommendation:

- There are insufficient data to recommend either for or against the routine use of extracorporeal membrane oxygenation (ECMO) for patients with COVID-19 and refractory hypoxemia **(BIII)**.

Rationale

While ECMO may serve as an effective short-term rescue therapy in patients with severe acute respiratory distress syndrome and refractory hypoxemia, there is no conclusive evidence that ECMO is responsible for better clinical outcomes in patients who received ECMO than in patients who did not receive ECMO.[1-4]

ECMO is used by some experts, when available, for patients with refractory hypoxemia despite optimization of ventilation strategies and adjunctive therapies. Ideally, clinicians who are interested in using ECMO should either try to enter their patient 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:

- Extracorporeal Life Support Organization
- Clinical trials evaluating ECMO in patients with COVID-19 on *ClinicalTrials.gov*.

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Potential Antiviral Drugs Under Evaluation for the Treatment of COVID-19

(Last updated June 16, 2020)

Summary Recommendations

There are no Food and Drug Administration (FDA)-approved drugs for the treatment of COVID-19, although remdesivir, an investigational antiviral drug, is available through an FDA emergency use authorization. Definitive clinical trial data are needed to identify safe and effective treatments for COVID-19. Such data are beginning to emerge. In this table, the COVID-19 Treatment Guidelines Panel (the Panel) provides recommendations on 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 the antiviral agents that are currently being evaluated for the treatment of COVID-19, see Tables 2a and 2b.

Remdesivir

Recommendations for Hospitalized Patients with Severe COVID-19:

- The Panel recommends the investigational antiviral agent **remdesivir** for treatment of COVID-19 in hospitalized patients with SpO_2 ≤94% on ambient air (at sea level) or those who require supplemental oxygen **(AI)**.
- The Panel recommends **remdesivir** for treatment of COVID-19 in patients who are on mechanical ventilation or extracorporeal membrane oxygenation (ECMO) **(BI)**.

Recommendation for Duration of Therapy in Patients with Severe COVID-19 Who Are Not Intubated:

- The Panel recommends that hospitalized patients with severe COVID-19 who are not intubated receive 5 days of **remdesivir (AI)**.

Recommendation for Duration of Therapy for Mechanically Ventilated Patients, Patients on ECMO, or Patients Who Have Not Shown Adequate Improvement After 5 Days of Therapy:

- There are insufficient data on the optimal duration of therapy for mechanically ventilated patients, patients on ECMO, or patients who have not shown adequate improvement after 5 days of therapy. In these groups, some experts extend the total **remdesivir** treatment duration to up to 10 days **(CIII)**.

Recommendation for Patients with Mild or Moderate COVID-19:

- There are insufficient data for the Panel to recommend for or against **remdesivir** for the treatment of patients with mild or moderate COVID-19.

Chloroquine/Hydroxychloroquine:

- The Panel **recommends against** the use of **chloroquine** or **hydroxychloroquine** for the treatment of COVID-19, except in a clinical trial **(AII)**.
- The Panel **recommends against** the use of **high-dose chloroquine** (600 mg twice daily for 10 days) for the treatment of COVID-19 **(AI)**.

Other Antiviral Drugs:

- The Panel **recommends against** using the following drugs to treat COVID-19 except in a clinical trial:
  - The combination of **hydroxychloroquine plus azithromycin (AIII)**, because of the potential for toxicities.
  - **Lopinavir/ritonavir (AI)** or **other HIV protease inhibitors (AIII)**, because of unfavorable pharmacodynamics and because clinical trials have not demonstrated a clinical benefit in patients with COVID-19.

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

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion

Remdesivir

(Last updated June 11, 2020)

Recommendations for Hospitalized Patients with Severe COVID-19

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends the investigational antiviral agent **remdesivir** for treatment of COVID-19 in hospitalized patients with SpO_2 ≤94% on ambient air (at sea level) or those who require supplemental oxygen **(AI)**.
- The Panel recommends **remdesivir** for treatment of COVID-19 in patients who are on mechanical ventilation or extracorporeal membrane oxygenation (ECMO) **(BI)**.

Rationale

Data from a multinational, randomized, placebo-controlled trial (the Adaptive COVID-19 Treatment Trial [ACTT]) of hospitalized patients with COVID-19 showed that patients with severe disease who were randomized to receive remdesivir had a shorter time to clinical recovery than those who received placebo.[1] The benefit of remdesivir on reducing time to recovery was clearest in the subgroup of hospitalized patients with severe disease who were not intubated but who required supplemental oxygen. In the preliminary analysis of ACTT, there was no observed improvement in the time to recovery among those who were mechanically ventilated, but the follow-up period may have been too short to have shown a difference.

Recommendation for Duration of Therapy in Patients with Severe COVID-19 Who Are Not Intubated

- The Panel recommends that hospitalized patients with severe COVID-19 who are not intubated receive 5 days of **remdesivir (AI)**.

Rationale

Data from a multinational, open-label trial of hospitalized patients with severe COVID-19 showed that remdesivir treatment for 5 or 10 days had similar clinical benefit in patients who were not on mechanical ventilation or ECMO.[2]

Recommendation for Duration of Therapy for Mechanically Ventilated Patients, Patients on ECMO, or Patients Who Have Not Shown Adequate Improvement After 5 Days of Therapy

- There are insufficient data on the optimal duration of therapy for mechanically ventilated patients, patients on ECMO, or patients who have not shown adequate improvement after 5 days of therapy. In these groups, some experts extend the total **remdesivir** treatment duration to up to 10 days **(CIII)**.

Rationale

Because the trial that compared 5 days to 10 days of remdesivir excluded people who were mechanically ventilated or on ECMO, the optimal duration of therapy in this population is not known. Similarly, the optimal duration of therapy for people who do not improve after 5 days of receiving remdesivir is unclear. In the absence of data, some experts may consider extending the total treatment duration of remdesivir for up to 10 days in people who are on mechanical ventilation or ECMO and in those who do not improve after 5 days of remdesivir.[3]

Recommendation for Patients with Mild or Moderate COVID-19

- There are insufficient data for the Panel to recommend for or against **remdesivir** for the treatment of patients with mild or moderate COVID-19.

Rationale

In the preliminary analysis of ACTT, there was no observed benefit for remdesivir in people with mild or moderate COVID-19; however, the number of people in this category was relatively small. Remdesivir is being evaluated in another clinical trial for the treatment of patients with moderate COVID-19; complete data from this trial are expected soon. The Food and Drug Administration (FDA) emergency use authorization (EUA) for remdesivir limits its use to people with severe COVID-19.

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

Remdesivir is an intravenous (IV) investigational nucleotide prodrug of an adenosine analog. It has demonstrated *in vitro* activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),[4] and *in vitro* and *in vivo* activity (based on animal studies) against SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV).[5-7] Remdesivir binds to the viral RNA-dependent RNA polymerase, inhibiting viral replication through premature termination of RNA transcription.

Preclinical studies show that remdesivir improves disease outcomes and reduces levels of SARS-CoV in mice.[5] When given as prophylaxis or therapy, remdesivir also reduces MERS-CoV levels and lung injury in mice. In a rhesus macaque model of MERS-CoV infection, prophylactic remdesivir prevented MERS-CoV clinical disease.[7] When given to rhesus macaques 12 hours after inoculation with MERS-CoV, remdesivir reduced viral replication and the severity of lung disease in treated animals compared to control animals. In a rhesus macaque model of SARS-CoV-2 infection, remdesivir treatment was started soon after inoculation in six of 12 monkeys. The remdesivir-treated animals had lower lung virus levels and less lung damage than the control animals.[8]

Clinical Data to Date

Multinational Randomized Controlled Trial of Remdesivir Versus Placebo in Hospitalized Patients

Study Design

ACTT is a National Institutes of Health-sponsored, multinational, randomized, double-blind, placebo-controlled trial in hospitalized adults with COVID-19.[1] Participants were randomized 1:1 to receive IV remdesivir or placebo for 10 days. The primary study endpoint was time to clinical recovery, which was defined as either discharge from the hospital or hospitalization for infection control purposes only. Severity of illness at baseline and at Day 15 was assessed using an ordinal scale:

3. Not hospitalized, no limitations
4. Not hospitalized, with limitations
5. Hospitalized, no active medical problems
6. Hospitalized, not on oxygen
7. Hospitalized, on oxygen
8. Hospitalized, on high-flow oxygen or noninvasive mechanical ventilation
9. Hospitalized, on mechanical ventilation or ECMO
10. Death

Study Population

The study population consisted of hospitalized patients aged ≥18 years with laboratory-confirmed SARS-CoV-2 infection. Patients were enrolled if they met at least one of the following conditions:

- The patient had pulmonary infiltrates, as determined by radiographic imaging;
- SpO_2 was ≤94% on ambient air;
- The patient required supplemental oxygen;
- The patient was on mechanical ventilation; *or*
- The patient was on ECMO.

The study excluded individuals who had alanine aminotransaminase (ALT) or aspartate aminotransaminase (AST) levels >5 times the upper limit of normal (ULN), those who had an estimated glomerular filtration rate (eGFR) <30 mL/min, and those who were pregnant or breastfeeding.

Preliminary Results

Participant Characteristics:

- Of 1,063 enrolled participants, 1,059 had preliminary results available for analysis (n = 538 for the remdesivir group; n = 521 for the placebo group).
- The mean age was 58.9 years; 64.3% of participants were male, 53.2% were white, and 79.8% were enrolled in North America.
- 52.1% of participants had two or more co-morbidities; 37% were obese (mean body mass index 30.6 kg/m2).
- The median time from symptom onset to randomization was 9 days (interquartile range [IQR] 6–12 days).

Follow-Up:

- At the time of the preliminary analysis, 391 remdesivir recipients and 340 placebo recipients had completed the study through Day 29, recovered, or died.
- Eight remdesivir recipients and nine placebo recipients terminated the study prior to Day 29.
- 132 remdesivir recipients and 169 placebo recipients had not recovered and had not completed the Day 29 follow-up visit at the time of this analysis.

Study Endpoint Analyses:

- Remdesivir significantly reduced time to recovery compared to placebo (median time to recovery 11 days vs. 15 days, respectively; recovery rate ratio 1.32; 95% confidence interval [CI], 1.12–1.55; $P < 0.001$).
- Clinical improvement based on the ordinal scale outlined above was significantly higher in patients who received remdesivir than in those who received placebo at Day 15 (odds ratio 1.50; 95% CI, 1.18–1.91; $P < 0.001$).
- The benefit of remdesivir on reducing time to recovery was clearest in the subgroup of hospitalized patients who required supplemental oxygenation at study enrollment (ordinal scale 5; n = 421).
- Among patients who were on mechanical ventilation or ECMO at enrollment (ordinal scale 7; n = 272), there was no observed difference between the remdesivir and placebo groups in time to recovery (recovery rate ratio 0.95; 95% CI, 0.64–1.42).

- Among patients who were classified as having mild to moderate disease at enrollment, there was no difference in the median time to recovery between the remdesivir and placebo groups (recovery rate ratio 1.09; 95% CI, 0.73–1.62; n = 119). Mild to moderate disease was defined as SpO_2 >94% on ambient air and respiratory rate <24 bpm without supplemental oxygen.
- The mortality estimate by Day 14 was lower in the remdesivir arm than in the placebo arm (7.1% vs. 11.9%, respectively), but the difference was not statistically significant (hazard ratio [HR] 0.70; 95% CI, 0.47–1.04).
- The use of remdesivir was associated with a shorter time to recovery regardless of the duration of symptoms prior to randomization (≤10 days vs. >10 days).
- The percentages of participants who experienced serious adverse events (AEs) were similar in the remdesivir and placebo groups (21.1% vs. 27.0%, respectively).
- Transaminase elevations occurred in 4.1% of remdesivir recipients and 5.9% of placebo recipients.

Limitations

- At the time of publication, the full dataset was not available for analysis.

Interpretation

In patients with severe COVID-19, remdesivir reduced the time to clinical recovery. The benefit of remdesivir was most apparent in hospitalized patients who were not intubated but who required supplemental oxygen. There was no observed benefit of remdesivir in those who were mechanically ventilated, but the follow-up period may have been too short to see a difference between the remdesivir and placebo groups. There was no observed benefit of remdesivir in patients with mild or moderate COVID-19, but the number of participants in these categories was relatively small.

Multinational Randomized Trial of Different Durations of Remdesivir Treatment in Hospitalized Patients

Study Design

This was a manufacturer-sponsored, multinational, randomized, open-label trial in hospitalized adolescents and adults with COVID-19. Participants were randomized 1:1 to receive either 5 days or 10 days of IV remdesivir. The primary study endpoint was clinical status at Day 14, which was assessed using a seven-point ordinal scale:[2]

1. Death
2. Hospitalized, on invasive mechanical ventilation or ECMO
3. Hospitalized, on noninvasive ventilation or high-flow oxygen devices
4. Hospitalized, requiring low-flow supplemental oxygen
5. Hospitalized, not requiring supplemental oxygen, but requiring ongoing medical care for COVID-19 or for other reasons
6. Hospitalized, not requiring supplemental oxygen or ongoing medical care (other than the care that was specified in the protocol for remdesivir administration)
7. Not hospitalized

Study Population

The study enrolled hospitalized patients aged ≥12 years with reverse transcription polymerase chain reaction (RT-PCR)-confirmed SARS-CoV-2 infection and radiographic evidence of pulmonary infiltrates. Patients in this study had either SpO_2 ≤94% on ambient air or were receiving supplemental

oxygen. The study excluded patients who were receiving mechanical ventilation or ECMO or who had multiorgan failure, ALT or AST levels >5 times ULN, or an estimated creatinine clearance of <50 mL/min. Patients were also excluded if they had received an agent with putative anti-SARS-CoV-2 activity within 24 hours of starting treatment in the trial.

Results

Participant Characteristics:

- Of 402 randomized participants, 397 began 5 days (n = 200) or 10 days (n = 197) of remdesivir treatment.
- In the 5-day group, the median age was 61 years; 60% of participants were male, and 71% were white. In the 10-day group, the median age was 62 years; 68% of participants were male, and 70% were white. The frequency of coexisting conditions was similar in both groups.
- The median time from symptom onset to the first dose of remdesivir was 8 days in the 5-day group and 9 days in the 10-day group. The median duration of hospitalization before the first remdesivir dose was 2 days in both groups.
- At baseline, patients in the 10-day group had worse clinical status (based on the ordinal scale distribution outlined above) than those in the 5-day group ($P = 0.02$).
- A few patients were on mechanical ventilation: four (2%) were assigned to the 5-day group, and nine (5%) were assigned to the 10-day group. Although mechanical ventilation was an exclusion criterion for enrollment, some patients were intubated between screening and treatment initiation; others were protocol deviations.
- 172 participants (86%) in the 5-day group completed a median of 5 days of treatment, and 86 (44%) in the 10-day group completed a median of 9 days of treatment.

Study Endpoint Analyses:

- 65% of patients in the 5-day group and 54% of those in the 10-day group had a two-point improvement in clinical status on the ordinal scale.
- After adjusting for imbalances in the baseline clinical status, the Day 14 distribution in clinical status on the ordinal scale was similar in the 5-day and 10-day groups ($P = 0.14$).
- The time to clinical improvement of at least two levels on the ordinal scale (median day of 50% cumulative incidence) was similar in the 5-day and 10-day groups (10 days vs. 11 days, respectively).
- The median durations of hospitalization among patients who were discharged on or before Day 14 were similar in the 5-day group (7 days; IQR 6–10 days) and the 10-day group (8 days; IQR 5–10 days).
- By Day 14, 120 patients (60%) in the 5-day group had been discharged and 16 (8%) had died; in the 10-day group, 103 patients (52%) had been discharged and 21 (11%) had died.
- Serious AEs were more common in the 10-day group (35%) than in the 5-day group (21%). Four percent of patients in the 5-day group and 10% of patients in the 10-day group stopped treatment because of AEs.

Limitations

- This was an open-label trial without a placebo control group, so the clinical benefit of remdesivir could not be assessed.
- There were baseline imbalances in the clinical statuses of participants in the 5-day and 10-day groups. At the start of the study, more patients in the 10-day group than in the 5-day group were

receiving noninvasive ventilation or high-flow oxygen (30% vs. 24%, respectively), and fewer patients in the 10-day group than in the 5-day group were not receiving supplemental oxygen (11% vs. 17%, respectively).

Interpretation

In hospitalized patients with COVID-19 who were not on mechanical ventilation or ECMO, remdesivir treatment for 5 or 10 days had similar clinical benefit. Because this trial only evaluated a few patients who were on mechanical ventilation, the appropriate duration of remdesivir treatment for critically ill patients is still unclear.

Randomized Controlled Trial of Remdesivir Versus Placebo for Severe COVID-19 in China

Study Design

This was a multicenter, double-blind, randomized, placebo-controlled trial that evaluated patients with severe COVID-19 in China.[9] Patients were randomized 2:1 to receive IV remdesivir or normal saline placebo for 10 days. Concomitant use of lopinavir/ritonavir, corticosteroids, and interferons were allowed. The primary study endpoint was time to clinical improvement, defined as improvement on an ordinal scale or discharged alive from the hospital, whichever came first. The planned sample size was 453 patients.

Participant Population

This study enrolled hospitalized adults with laboratory-confirmed COVID-19 whose time from symptom onset to randomization was <12 days, whose O_2 saturation was ≤94% on ambient air or whose PaO_2/FiO_2 was <300 mm Hg, and who had radiographically confirmed pneumonia.

Results

- 237 hospitalized patients were enrolled and randomized to treatment from February 6, 2020, to March 12, 2020; 158 patients were randomized to receive remdesivir and 79 patients were randomized to receive placebo. The study was stopped before the target enrollment was reached due to control of the COVID-19 outbreak in China.
- The median age of the participants was 65 years; 56% of the participants in the remdesivir arm and 65% of the participants in the placebo arm were male.
- There were more patients with hypertension, diabetes, or coronary artery disease in the remdesivir arm than in the placebo arm.
- At Day 1, 83% of the participants required supplemental oxygen by nasal cannula or mask; only one participant required mechanical ventilation or ECMO.
- The median time from symptom onset to randomization was 9 days in the remdesivir group and 10 days in the placebo group.
- 65% of the participants in the remdesivir group and 68% of the participants in the placebo group received corticosteroids.
- 28% of the participants in the remdesivir group and 29% of the participants in the placebo group received lopinavir/ritonavir.
- 29% of the participants in the remdesivir arm and 38% of the participants in the placebo arm received interferon alfa-2b.

Study Endpoints

- There was no difference in the time to clinical improvement between the remdesivir and placebo groups (a median of 21 days vs. 23 days, respectively; HR 1.23; 95% CI, 0.87–1.75).

- For patients who started the study drug within 10 days of symptom onset, faster time to clinical improvement was seen in the remdesivir arm than in the placebo arm (a median of 18.0 days vs. 23.0 days, respectively; HR 1.52, 95% CI, 0.95–2.43); however, this was not statistically significant.
- The 28-day mortality rate was similar for the two study arms (14% and 13% of participants in the remdesivir arm and placebo arm, respectively).
- There was no difference between the groups in SARS-CoV-2 viral load at baseline, and the rate of decline over time was similar between the two groups.
- The number of participants who experienced AEs was similar in the two groups (66% and 64% of participants in the remdesivir and placebo groups, respectively).
- More participants in the remdesivir arm than in the placebo arm discontinued therapy due to AEs (12% vs. 5% of participants in the remdesivir and placebo groups, respectively).

Limitations

- The study was terminated early; as a result, the sample size did not have sufficient power to detect differences in clinical outcomes.
- The use of concomitant medications (corticosteroids, lopinavir/ritonavir, interferon) may have obscured the effects of remdesivir.

Interpretation

There was no difference in time to clinical improvement, 28-day mortality, or rate of viral clearance between the remdesivir-treated patients and the placebo-treated patients.

Uncontrolled Case Series from Remdesivir Compassionate Use Program

In an uncontrolled case series of 53 hospitalized people with COVID-19, most patients needed less oxygen support after receiving compassionate use remdesivir. There was no comparison group, however, so it is not possible to assess whether the improvement was the result of using remdesivir.[10]

Clinical Trials

Multiple clinical trials are currently underway or in development. Please check *ClinicalTrials.gov* for the latest information.

Monitoring, Adverse Effects, and Drug-Drug Interactions

Remdesivir can cause gastrointestinal symptoms (e.g., nausea, vomiting), elevated transaminase levels, and prothrombin time elevation (without change in international normalized ratio). *In vitro*, remdesivir is a cytochrome P450 (CYP) 3A4, CYP2C8, and CYP2D6 substrate. Coadministering remdesivir with inhibitors of these enzymes is not expected to have a significant impact on remdesivir concentrations. Remdesivir concentration may be affected by strong CYP inducers, but the interaction is not expected to be clinically significant.[11]

Because the remdesivir formulation contains renally cleared sulfobutylether-beta-cyclodextrin sodium, patients with an eGFR <50 mL/min are excluded from some clinical trials (some trials have a cutoff of eGFR <30 mL/min).

Considerations in Pregnancy

- Use remdesivir in pregnant patients only when the potential benefit justifies the potential risk to the mother and the fetus.[3]

- The safety and effectiveness of remdesivir for COVID-19 treatment have not been evaluated in pregnant patients. Remdesivir should not be withheld from pregnant patients if it is otherwise indicated.
- Remdesivir is available through the FDA EUA for adults and children and through a compassionate use program for pregnant women with COVID-19.
- In a randomized controlled Ebola treatment trial of therapies that included remdesivir, among 98 female participants who received remdesivir, six had a positive pregnancy test. The obstetric and neonatal outcomes were not reported in the study.[12]

Considerations in Children

- The safety and effectiveness of remdesivir for COVID-19 treatment have not been evaluated in pediatric patients.
- Remdesivir is available through an FDA EUA for adults and children and through a compassionate use program for patients aged <18 years with COVID-19.
- In the same randomized controlled trial for the treatment of Ebola virus infection, 41 pediatric patients aged <7 days to <18 years received remdesivir.[12] The safety and clinical outcomes in children were not reported separately in the published results for the trial.

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Chloroquine or Hydroxychloroquine

(Last updated June 16, 2020)

Overall Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of **chloroquine** or **hydroxychloroquine** for the treatment of COVID-19, except in a clinical trial **(AII)**.
- 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 have been evaluated in small randomized clinical trials, case series, and observational studies (as described below). Data from large randomized controlled trials are necessary to definitively determine the efficacy of chloroquine and hydroxychloroquine in treating COVID-19.

A large, retrospective, observational study that evaluated the use of hydroxychloroquine has shown no evidence of benefit in patients with COVID-19. Clinical outcomes in that study included death and the need for mechanical ventilation.[1] Reports have documented serious dysrhythmias in patients with COVID-19 who were treated with chloroquine or hydroxychloroquine, often in combination with azithromycin and other medicines that prolong the QTc interval. **Given the risk of dysrhythmias, the Food and Drug Administration (FDA) cautions against the use of chloroquine or hydroxychloroquine for the treatment of COVID-19 outside of a hospital or clinical trial.**[2] When chloroquine or hydroxychloroquine is used, clinicians should monitor the patient for adverse effects (AEs), especially prolonged QTc interval **(AIII)**.

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 comparative trial compared high-dose chloroquine and low-dose chloroquine in patients with 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.[3]

Background

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

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

- 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.[4]
- Chloroquine inhibits glycosylation of the cellular angiotensin-converting enzyme 2 receptor, which may interfere with binding of SARS-CoV to the cell receptor.[5]
- *In vitro*, both chloroquine and hydroxychloroquine may block the transport of SARS-CoV-2 from

early endosomes to endolysosomes, which may be required for release of the viral genome.[6]

- Both chloroquine and hydroxychloroquine have immunomodulatory effects.

Clinical Data for COVID-19

The available clinical data on the use of chloroquine and hydroxychloroquine to treat COVID-19 mostly come from patients with mild, and, in some cases, moderate disease. Clinical data on the use of these drugs in patients with severe and critical COVID-19 are limited. The clinical data are summarized below.

Please see the Hydroxychloroquine plus Azithromycin section for additional clinical data on hydroxychloroquine.

Chloroquine

High-Dose Versus Low-Dose Chloroquine

A randomized, double-blind, Phase 2b study compared two different chloroquine regimens for the treatment of COVID 19: high-dose chloroquine (600 mg twice daily for 10 days) versus low-dose chloroquine (450 mg twice daily for 1 day followed by 450 mg for 4 days). The study participants were hospitalized adults with suspected severe COVID-19 (respiratory rate >24 rpm, heart rate >125 bpm, oxygen saturation <90%, and/or shock).[3] All patients received ceftriaxone plus azithromycin; 89.6% of patients also received oseltamivir. Of note, both azithromycin and oseltamivir can increase the QTc interval.

The primary outcome measure for this analysis was mortality at 13 days after treatment initiation. The planned study sample size was 440 participants, which was enough to show a reduction in mortality by 50% with high-dose chloroquine. The study was stopped by the data safety and monitoring board after 81 patients were enrolled into the study.

Results:

- 41 and 40 patients were randomized into the high-dose and low-dose arms, respectively.
- The overall fatality rate was 27.2%.
- Mortality by Day 13 was higher in the high-dose arm than in the low-dose arm (death occurred in 16 of 41 patients [39%] vs. in six of 40 patients [15%]; $P = 0.03$). This difference was no longer significant after controlling for age (odds ratio 2.8; 95% confidence interval [CI], 0.9–8.5).
- Overall, QTcF >500 ms occurred more frequently among patients in the high-dose arm (18.9%) than in the low-dose arm (11.1%). Among those with confirmed COVID-19, QTcF >500 ms occurred more frequently in the high-dose arm (24.1%) than in the low-dose arm (3.6%).
- Two patients in the high-dose arm experienced ventricular tachycardia before death.

Limitations:

- More older patients and more patients with a history of heart disease were randomized to the high-dose arm than to the low-dose arm.

Interpretation

Despite the small number of patients enrolled, this study raises concerns about an increased risk of mortality when high-dose chloroquine (600 mg twice daily) is administered in combination with azithromycin and oseltamivir.

Chloroquine Versus Lopinavir/Ritonavir

In a small randomized controlled trial in China, 22 hospitalized patients with COVID-19 (none critically ill) were randomized to receive oral chloroquine 500 mg twice daily or lopinavir 400 mg/ritonavir 100 mg twice daily for 10 days.[7] Patients with a history of heart disease (chronic disease and a history of arrhythmia), or kidney, liver, or hematologic disease were excluded from participation. The primary study outcome was SARS-CoV-2 polymerase chain reaction (PCR) negativity at Days 10 and 14. Secondary outcomes included improvement of lung computed tomography (CT) scan at Days 10 and 14, discharge at Day 14, and clinical recovery at Day 10, as well as safety (which was determined by evaluating study drug-related AEs).

Results:

- 10 patients received chloroquine and 12 patients received lopinavir/ritonavir. At baseline, patients had good peripheral capillary oxygen saturation (SpO_2) (97% to 98%).
- Compared to the lopinavir/ritonavir-treated patients, the chloroquine-treated patients had a shorter duration from symptom onset to initiation of treatment (2.5 days vs. 6.5 days, $P < 0.001$).
- Though not statistically significant, patients in the chloroquine arm were younger (median age 41.5 years vs. 53.0 years, $P = 0.09$). Few patients had co-morbidities.
- At Day 10, 90% of the chloroquine-treated patients and 75% of the lopinavir/ritonavir-treated patients had a negative SARS-CoV-2 PCR test result. At Day 14, the percentages for the chloroquine-treated patients and the lopinavir/ritonavir-treated patients were 100% and 91.2%, respectively.
- At Day 10, 20% of the chloroquine-treated patients and 8.3% of the lopinavir/ritonavir-treated patients had CT scan improvement. At Day 14, the percentages for the chloroquine-treated patients and the lopinavir/ritonavir-treated patients were 100% and 75%, respectively.
- At Day 14, 100% of the chloroquine-treated patients and 50% of the lopinavir/ritonavir-treated patients were discharged from the hospital.
- The risk ratios of these outcome data cross 1, and the results were not statistically significant.
- Both chloroquine and lopinavir/ritonavir were generally well-tolerated.

Limitations:

- The trial sample size was very small, and the participants were fairly young.
- The chloroquine-treated patients were younger and had fewer symptoms prior to treatment initiation, which are variables that could have affected the study protocol-defined outcomes.
- Patients who had chronic co-morbidities and who were critically ill were excluded from the study.

Interpretation

In this small randomized controlled trial, chloroquine and lopinavir/ritonavir showed similar efficacy in treating COVID-19.

Hydroxychloroquine

Observational Study of Hydroxychloroquine at a Large Medical Center in New York City

This observational study evaluated 1,376 consecutive adults with COVID-19 who were admitted to a large New York City hospital (after excluding 70 patients who died or who were transferred within 24 hours after presenting to the emergency department). The study assessed the time from study baseline (24 hours after patients arrived at the emergency department) to intubation or death based on whether

the patient received hydroxychloroquine at baseline or during follow-up. Patients who received hydroxychloroquine were prescribed a twice-daily dose of hydroxychloroquine 600 mg on the first day and 400 mg daily for 4 additional days; this was based on the clinical guidance of the hospital.[1]

Results:

- 811 patients (58.5%) received hydroxychloroquine and 565 (41.1%) did not.
- Patients who received hydroxychloroquine were older and more likely to have hypertension (49.1% vs. 6.7%) and to be on systemic steroids (26.6% vs. 10.1%) compared with those who did not receive hydroxychloroquine.
- Patients who received hydroxychloroquine were more likely to receive concomitant azithromycin (59.9% vs. 22.5%) and/or other antibiotics (74.5% vs. 54.0%) compared with those who did not receive hydroxychloroquine.
- Patients who received hydroxychloroquine had higher levels of inflammatory markers.
- Hydroxychloroquine-treated patients had more severe hypoxia, with a lower PaO_2/FiO_2 ratio at baseline than patients who did not receive hydroxychloroquine (median of 233 mm Hg vs. 360 mm Hg).
- Most patients (85.9%) received hydroxychloroquine within 48 hours of presentation.
- Using propensity scores to adjust for major predictors of respiratory failure and inverse probability weighting, the study demonstrated that hydroxychloroquine use was not associated with intubation or death (hazard ratio [HR] 1.04; 95% CI, 0.82–1.32).
- There was also no association between concomitant use of azithromycin and the composite endpoint of intubation or death (HR 1.03; 95% CI, 0.81–1.31).

Limitations:

- Despite the large size of this study, it suffers from the inherent limitations of an observational study. These include residual confounding from confounding variables that were unrecognized and/or unavailable for analysis.

Interpretation

The use of hydroxychloroquine for treatment of COVID-19 was not associated with harm or benefit in a large observational study.

Retrospective Observational Cohort from the United States Veterans Health Administration

This study has not been peer reviewed.

An observational, retrospective cohort study analyzed data from patients with confirmed COVID-19 who were hospitalized at the United States Veterans Health Administration medical centers between March 9, 2020, and April 11, 2020.[8] Patients were categorized as having received either hydroxychloroquine, hydroxychloroquine plus azithromycin, or no hydroxychloroquine. Doses and duration of hydroxychloroquine or azithromycin use were not specified. All patients also received standard supportive management for COVID-19. The primary endpoints were death and the need for mechanical ventilation. Associations between treatment and outcomes were determined using propensity score adjustment, including demographic, co-morbid, and clinical data (including predictors of COVID-19 disease severity). Patients were included in the analysis if body mass index, vital signs, and discharge disposition were noted in their medical records.

Results:

- 368 patients were eligible for analysis. The patients were categorized into three treatment groups:

hydroxychloroquine (n = 97; median age of 70 years), hydroxychloroquine plus azithromycin (n = 113; median age of 68 years), or no hydroxychloroquine (n = 158; median age of 69 years). All patients were male.

- 70 patients died; 35 of those who died (50%) were not receiving mechanical ventilation.
- No difference was observed between the groups in the risk of mechanical ventilation.
- Compared to the no hydroxychloroquine group, the risk of death from any cause was higher in the hydroxychloroquine group (adjusted HR 2.61; 95% CI, 1.10–6.17; $P = 0.03$), but not in the hydroxychloroquine plus azithromycin group (adjusted HR 1.14; 95% CI, 0.56–2.32, $P = 0.72$).
- There was no between-group difference in the risk of death after ventilation.

Limitations:

- The patient population was entirely male.
- The dose and duration of administration for hydroxychloroquine and azithromycin were not included in the report. Patients were included if they received a single dose of either or both drugs.
- Propensity score adjustment was used to account for differences between the groups, but the possibility of residual confounding cannot be excluded, as patients who were more ill may have been more likely to receive hydroxychloroquine.
- No imaging data were presented; severity of chest X-ray findings could predict worse outcomes.
- The use of other antiviral or immunomodulatory agents was not reported.
- The reason for the high mortality rate among patients who did not receive mechanical ventilation is not clear, especially as most of these patients appear to have had mild/moderate disease at admission.

Interpretation

This study showed no beneficial effect of hydroxychloroquine plus azithromycin for the treatment of COVID-19 and a possible association between hydroxychloroquine and increased mortality; however, residual confounding may have affected the study results.

Randomized Controlled Trial of Hydroxychloroquine Versus Standard of Care for Mild/Moderate COVID-19

This multicenter, randomized, open-label trial compared hydroxychloroquine 1,200 mg once daily for 3 days followed by hydroxychloroquine 800 mg once daily for the rest of the treatment duration (2 weeks for patients with mild/moderate COVID-19 [99% of the patients] and 3 weeks for two patients with severe disease) versus standard of care (SOC).[9]

The primary outcome was negative PCR within 28 days. Secondary outcomes were alleviation of symptoms (resolution of fever, SpO_2 >94% on room air, resolution of respiratory symptoms), improvement in markers of inflammation (including C-reactive protein), and improvement of lung lesions on a chest X-ray within 28 days.

Results:

- 75 patients were enrolled in each study arm. Patients were randomized at a mean of 16.6 days after symptom onset.
- No difference was found between the hydroxychloroquine arm and the SOC arm in negative PCR conversion rate within 28 days (85.4% of participants vs. 81.3% of participants, respectively) or in time to negative PCR conversion (median of 8 days vs. 7 days, respectively).

- There was no difference in the probability of symptom alleviation between the groups in the intention-to-treat analysis.
- AEs occurred in 30% of the participants in the hydroxychloroquine arm (most commonly diarrhea) versus in 9% of the participants in the SOC arm.

Limitations:

- It is unclear how the overall rate of symptom alleviation was calculated.
- The duration of hydroxychloroquine use (2 weeks) was longer than in most other observational cohort studies or clinical trials for the treatment of COVID-19.
- The study did not reach the target sample size.

Interpretation

This study demonstrated no difference in viral clearance between hydroxychloroquine and SOC.

Observational Cohort of Hydroxychloroquine Versus No Hydroxychloroquine

This observational, retrospective cohort study analyzed data for adult patients who were hospitalized for COVID-19 pneumonia at four French tertiary care centers over a 2-week period (March 17–31, 2020). Patients aged 18 to 80 years were eligible if they had PCR-confirmed SARS-CoV-2 infection and required oxygen by mask or nasal cannula. Exclusion criteria included hydroxychloroquine initiation before hospitalization, receipt of another experimental COVID-19 treatment within 48 hours, organ failure that required immediate admission to the intensive care unit (ICU) or continuous care unit, admission with acute respiratory distress syndrome (ARDS) that required noninvasive ventilation with continuous positive airway pressure or mechanical ventilation, discharge from the ICU to standard care, or if a decision was made to limit or stop active treatments that were prescribed at admission. Patients in one treatment arm received a daily dose of hydroxychloroquine 600 mg within 48 hours of admission; patients in the other arm did not receive hydroxychloroquine during the same period. The decision to use hydroxychloroquine to treat a patient was based on local medical consensus and prescriber opinion, and was reportedly independent of patient characteristics. Patients were followed from baseline until death, loss to follow-up, or the end of follow-up on April 24, 2020. The primary outcome was survival without transfer to the ICU at Day 21. An inverse probability of treatment weighting approach was used to "emulate" randomization.[10]

Results:

- Of the 181 patients who were eligible for the analysis, 84 participants received hydroxychloroquine within 48 hours, eight received hydroxychloroquine beyond 48 hours, and 89 participants did not receive hydroxychloroquine.
- Co-morbidities were less common in the hydroxychloroquine group; overall initial COVID-19 severity was well balanced across the treatment arms.
- In the hydroxychloroquine group, 18% of the patients received concomitant azithromycin and 52% of the patients received amoxicillin/clavulanic acid.
- In the inverse probability of treatment weighted analysis, there was no difference in the primary outcome (survival rate without ICU transfer at Day 21) between the hydroxychloroquine group (76% of participants) and the non-hydroxychloroquine group (75% of participants). Similarly, there was no difference between the groups in the secondary outcomes of survival and survival without ARDS at Day 21.
- Among the 84 patients who received hydroxychloroquine within 48 hours, eight patients (10%) experienced electrocardiogram (ECG) changes that required treatment discontinuation at a median

of 4 days from the start of dosing, including seven patients with a QTc that prolonged >60 ms and one patient with new onset, first-degree atrioventricular block. None of these patients received azithromycin.

Limitations:

- This was a retrospective, nonrandomized study.

Interpretation

In this retrospective study, there was no difference in clinically important outcomes between patients who received hydroxychloroquine within 48 hours of hospital admission and those who did not.

A Case Series of Hydroxychloroquine Versus Control

In a case series from France, 26 hospitalized adults with SARS-CoV-2 infection categorized as asymptomatic or with upper or lower respiratory tract infection who received hydroxychloroquine 200 mg three times daily for 10 days were compared to 16 control individuals (i.e., those who refused treatment, did not meet eligibility criteria, or were from a different clinic).[11]

Results:

- Six patients in the hydroxychloroquine group were excluded from the analysis for the following reasons:
  - One patient died.
  - Three patients were transferred to the ICU.
  - One patient stopped taking the study drug due to nausea.
  - One patient withdrew from the study.
- Six patients also received azithromycin.
- By Day 6, nasopharyngeal (NP) PCRs were negative in 14 of 20 hydroxychloroquine-treated patients (70%) and two of 16 controls (12.5%).
- Among the hydroxychloroquine patients, eight of 14 patients (57.1%) who received only hydroxychloroquine and six of six patients (100%) who received hydroxychloroquine and azithromycin had negative NP PCRs by Day 6.
- Clinical outcomes were not reported for all patients.

Limitations:

- There are several methodologic concerns with this case series:
  - The sample size of the series is small.
  - The criteria for enrollment of cases and controls is unclear.
  - Asymptomatic individuals were enrolled.
  - Exclusion of six hydroxychloroquine patients includes one death and three ICU transfers.
  - No clinical outcomes were reported; thus, the clinical significance of a negative PCR is unknown.
  - The reason for the addition of azithromycin for some patients is unclear.

Interpretation

Methodologic problems with this case series limit the ability to draw conclusions regarding the efficacy of hydroxychloroquine with or without azithromycin.

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 arrythmia, and cardiac deaths.
- 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], fluoroquinolone antibiotics)[12] should be used only if necessary. Consider using doxycycline rather than azithromycin as empiric therapy for atypical pneumonia.
- Baseline and follow-up ECGs are recommended when there are potential drug interactions with concomitant medications (e.g., azithromycin) or underlying cardiac diseases.[13]
- The risk-benefit ratio should be closely assessed for patients with cardiac disease, a history of ventricular arrhythmia, bradycardia (<50 beats per minute), 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.

There is no evidence that glucose-6-phosphate dehydrogenase (G6PD) deficiency is relevant for the use of hydroxychloroquine, and G6PD testing **is not recommended**.

With chloroquine use, there is a greater risk for hemolysis in patients with G6PD deficiency. Conduct G6PD testing before initiating chloroquine. Consider using hydroxychloroquine until G6PD test results are available. If the test results indicate that the patient is G6PD deficient, hydroxychloroquine should be continued.

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 coadministering 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).[14]

Considerations in Pregnancy

- Antirheumatic doses of chloroquine and hydroxychloroquine have been used safely in pregnant women with SLE.
- Hydroxychloroquine has not been associated with adverse pregnancy outcomes in ≥300 human pregnancies with exposure to the drug.
- A lower dose of chloroquine (500 mg once a week) is used for malaria prophylaxis in pregnancy.
- No dosing changes are necessary for chloroquine or hydroxychloroquine during pregnancy.

Considerations in Children

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

Drug Availability

- Hydroxychloroquine is approved by the FDA for the treatment of malaria, lupus erythematosus, and rheumatoid arthritis and is available commercially. Hydroxychloroquine is not approved for the treatment of COVID-19.
- Chloroquine is not available commercially in the United States.

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Hydroxychloroquine plus Azithromycin

(Last updated May 12, 2020)

Please also see the Hydroxychloroquine and Chloroquine sections, as some patients in those studies also received azithromycin as part of their treatment.

Recommendation:

- The Panel recommends against the use of **hydroxychloroquine plus azithromycin** for the treatment of COVID-19, except in the context of a clinical trial **(AIII)**.

Rationale for Recommendation

Chloroquine and hydroxychloroquine for COVID-19 have been used in small randomized trials and in some case series with conflicting study reports (as described above). 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.[1]

Clinical Data in COVID-19

Case Series of Hydroxychloroquine Plus Azithromycin

In a case series of 80 hospitalized patients with COVID-19 (including six patients from a previous study),[2] patients were treated with hydroxychloroquine sulfate 200 mg three times daily for 10 days plus azithromycin 500 mg for 1 day followed by 250 mg once daily for 4 days. Mean time from symptom onset to treatment was about 5 days. Outcomes evaluated included the need for oxygen therapy or intensive care unit (ICU) transfer after ≥3 days of therapy, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) level by polymerase chain reaction (PCR), SARS-CoV-2 culture (in a subset of patients; a convenience sample), and length of stay in the infectious diseases ward.[2]

Clinical Results:

- One (1.2%) patient died and three (3.8%) patients required ICU transfer, 12 (15%) patients required oxygen therapy.
- 65 (81.2%) patients were discharged to home or transferred to other units for continuing treatment; 14 (17.4%) patients remained hospitalized at the time the study results were published.

Laboratory Results:

- Nasopharyngeal (NP) SARS-CoV-2 PCR was negative in 83% of patients by Day 7 and 93% of patients by Day 8.
- In the subset of patients who had respiratory sample viral cultures performed at Day 5, results were negative for 97.5% of the samples.

Limitations:

- The trial's lack of a control group, which is particularly important because many people with mild disease improve in the absence of treatment.
- The definition of "discharge" varied.
- The lack of complete or longer-term follow-up.

Interpretation:

The multiple issues with the trial design and the lack of a comparison group limit the usefulness of this

study to inform recommendations.

Small Prospective Case Series of Hydroxychloroquine Plus Azithromycin

A prospective case series from France assessed eleven consecutive hospitalized patients with COVID-19.[3]

Results:

- Eight of the 11 patients had significant co-morbid conditions: obesity (2), solid cancer (3), hematological cancer (2), and HIV-infection (1).
- Ten of 11 patients were receiving supplemental oxygen upon treatment initiation.
- All patients were treated with hydroxychloroquine 600 mg once daily for 10 days and azithromycin 500 mg once daily for 1 day followed by 250 mg once daily for 4 days.
- Within 5 days, the condition of three patients worsened, including one patient who died and two patients who were transferred to the ICU.
- Adverse events: Hydroxychloroquine was discontinued in one patient due to QTc prolongation.
- Qualitative NP PCR remained positive at Days 5 and 6 after treatment initiation in 8 of 10 patients.

Limitations:

- This is a case series that included only 11 patients.

Interpretation:

In this small case series, most patients who received hydroxychloroquine plus azithromycin did not have rapid viral clearance.

Case Series of Changes in QTc Interval in Patients Who Received Hydroxychloroquine Plus Azithromycin

A case series in the United States reported changes in QTc interval in 84 patients with COVID-19 who received the combination of hydroxychloroquine 400 mg twice daily for 1 day, followed by 200 mg twice daily for 4 days, and azithromycin 500 mg once daily for 5 days.[4]

Results:

- 84 patients, 74% male, mean age 63 ± 15 years, 65% had hypertension, baseline serum creatinine 1.4 mg/dL, 13% required vasopressors, 11% had coronary artery disease.
- Among all the patients, 11% received neuropsychiatric drugs that may prolong QTc interval and 8% received other concomitant drugs (levofloxacin, lopinavir/ritonavir, or tacrolimus) that may prolong QTc.
- Four patients died, without arrhythmia.
- The mean baseline QTc was 435 ± 24 ms; the mean maximum QTc was 463 ± 32 ms.
- The mean time to maximum QTc was 3.6 ± 1.6 days; ECG follow-up was done for a mean of 4.3 days.
- 9 patients (11%) developed QTc >500 ms; the QTc increased by 40 to 60 ms and >60 ms in 18% and 12% of patients, respectively.

Limitations:

- Case series, descriptive

Interpretation:

This case series demonstrates that hydroxychloroquine and azithromycin in combination can prolong QTc,

and that use of the combination warrants careful monitoring.

Clinical Trials

Clinical trials to test the safety and efficacy of chloroquine or hydroxychloroquine with or without azithromycin in people who have or are at risk for COVID-19 are underway in the United States and internationally. Please check *ClinicalTrials.gov* for the latest information.

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Lopinavir/Ritonavir and Other HIV Protease Inhibitors

(Last updated May 12, 2020)

Recommendation:

- The Panel **recommends against** the use of **lopinavir/ritonavir (AI) or other HIV protease inhibitors (AIII)** for the treatment of COVID-19, except in the context of a clinical trial.

Rationale for Recommendation

The pharmacodynamics of HIV protease inhibitors raise concern regarding whether drug levels adequate to inhibit the SARS-CoV-2 protease can be achieved with oral dosing. Also, lopinavir/ritonavir was studied in a small randomized controlled trial in patients with COVID-19 with results that did not show efficacy (see below).

Lopinavir/Ritonavir

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

- Replication of SARS-CoV-2 depends on the cleavage of polyproteins into an RNA-dependent RNA polymerase and a helicase.[1] The enzymes responsible for this cleavage are two proteases, 3-chymotrypsin-like protease (3CLpro) and papain-like protease (PLpro).
- Lopinavir/ritonavir is an inhibitor of SARS-CoV 3CLpro *in vitr*o, and this protease appears highly conserved in SARS-CoV-2.[2,3]
- Although lopinavir/ritonavir has *in vitr*o activity against SARS-CoV, it is thought to have a poor selectivity index, indicating that higher than tolerable levels of the drug might be required to achieve meaningful inhibition *in vivo*.[4]
- Lopinavir is excreted in the gastrointestinal tract, and thus coronavirus-infected enterocytes might be exposed to higher concentrations of the drug.[5]

Clinical Data in COVID-19

Randomized Controlled Trial of Lopinavir/Ritonavir Versus Standard of Care

In a clinical trial that randomized 199 patients to lopinavir 400 mg/ritonavir 100 mg orally twice daily for 14 days or to standard of care (SOC), patients randomized to the lopinavir/ritonavir arm did not have a shorter time to clinical improvement.[6]

Results:

- There was a lower, but not statistically significant, mortality rate for the lopinavir/ritonavir group (19.2%) than for the SOC group (25.0%) and shorter ICU stay for those in the lopinavir/ritonavir group than in the SOC group (6 days vs. 11 days; difference = -5 days; 95% CI, -9 to 0).
- The duration of hospital stays and time to clearance of viral RNA from respiratory tract samples did not differ between the lopinavir/ritonavir and SOC arms.
- Nausea, vomiting, and diarrhea were all more frequent in the lopinavir/ritonavir-treated group.
- The study was powered only to show a fairly large effect.

Limitations:

- The study was not blinded, which may have affected the assessments of clinical improvement.
- The study was underpowered to show small effects.

Interpretation

A moderate-sized randomized trial failed to find a virologic or clinical benefit of lopinavir/ritonavir over standard of care.

Lopinavir/Ritonavir Versus Arbidol Versus Standard of Care

This study has not been peer reviewed.

In a trial of 86 hospitalized patients with mild-to-moderate COVID-19, 34 patients were randomized to lopinavir/ritonavir, 35 patients to the broad-spectrum antiviral Arbidol (available in Russia), and 17 patients to SOC.[7]

Results (Comparison of Lopinavir/Ritonavir to Standard of Care):

- The time to a negative SARS-CoV-2 nucleic acid pharyngeal swab was similar for patients receiving lopinavir/ritonavir (mean of 9 days [SD 5.0]) and for those receiving SOC (mean of 9.3 days [SD 5.2]).
- Progression to severe/critical status occurred among eight patients receiving lopinavir/ritonavir (24%) and two patients on SOC (12%).

Limitations:

- The trial had a small sample size.
- The effectiveness of Arbidol in treating COVID-19 is unknown.

Interpretation

The small sample size of this trial limits its usefulness.

Lopinavir/Ritonavir Versus Chloroquine

A small randomized study in China compared lopinavir/ritonavir to chloroquine. Please refer to the chloroquine section for the study description.[8]

Clinical Trials:

None in the United States

Monitoring, Adverse Effects, and Drug-Drug Interactions

- *Adverse Effects Include:*
  - Nausea, vomiting, diarrhea (common)
  - QTc prolongation
  - Hepatotoxicity
- Lopinavir/ritonavir is a potent inhibitor of CYP3A, and many medications metabolized by this enzyme may cause severe toxicity. Please refer to the Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV for a list of potential drug interactions.

Considerations in Pregnancy:

- There is wide experience with use of lopinavir/ritonavir in pregnant women with HIV, and the drug has a good safety profile.
- No evidence of human teratogenicity (can rule out a 1.5-fold increase in overall birth defects).
- Low placental transfer to the fetus. Please refer to the Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States.
- *Dosing:*

- Lopinavir/ritonavir oral solution contains 42.4% (volume/volume) alcohol and 15.3% (weight/volume) propylene glycol and **is not recommended** for use during pregnancy. Please refer to the Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States.
- Once daily lopinavir/ritonavir dosing **is not recommended** during pregnancy.

Considerations in Children:

- Lopinavir/ritonavir is approved for the treatment of HIV in infants, children, and adolescents.
- There are no data on the efficacy of lopinavir/ritonavir used to treat COVID-19 in pediatric patients.

Darunavir/Cobicistat or Darunavir/Ritonavir

Rationale for Use, Proposed Mechanism of Action for COVID-19:

- Inhibition of the 3CLpro enzyme of SARS-CoV-2 and possibly also inhibition of the PLpro enzyme.
- In an *in vitro* study, darunavir did not show activity against SARS-CoV-2.[9]
- Results from an unpublished randomized controlled trial of 30 patients in China showed that darunavir/cobicistat was not effective in the treatment of COVID-19.[10]

Clinical Trials:

None in the United States

Other HIV Protease Inhibitors, Including Atazanavir

There are no data from clinical trials that support the use of other HIV protease inhibitors to treat COVID-19.

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Table 2a. Potential Antiviral Agents Under Evaluation for Treatment of COVID-19: Clinical Data to Date

(Last updated June 11, 2020)

Information presented in this table may include data from pre-prints or non-peer reviewed articles. This table will be updated as new information becomes available.

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date (Find clinical trials on ClinicalTrials.gov)
Azithromycin **Note:** Studies on COVID-19 use AZM with HCQ.	• Mycobacterial (nontuberculous) infection • STIs and various bacterial infections[1]	**Proposed Antiviral Effects:** • Induction of IFN-stimulated genes, attenuating viral replication[2] **Immunomodulatory Effect:** • Enhanced neutrophil activation[3] **Anti-Inflammatory Effects:** • Attenuation of inflammatory cytokines (IL-6 and IL-8) in epithelial cells and inhibition of fibroblast growth factor in airway smooth muscle cells[2]	• AZM is studied for treatment of COVID-19 only in combination with HCQ. • Please see the description of study results in the Hydroxychloroquine Plus Azithromycin section below and in Hydroxychloroquine Plus Azithromycin.
Chloroquine	• Malaria • Extra-intestinal amebiasis	**Proposed Antiviral Effects:** • *In vitro* antiviral activity by increasing the pH of intracellular vacuoles and altering protein degradation pathways, thereby interfering with the virus/cell fusion and glycosylation of cellular receptors[4,5] • Inhibits glycosylation of the cellular ACE2 receptor, which may interfere with the binding of the virus to the cell receptor[6] **Immunomodulatory Effect:** • CQ may lead to a reduction in pro-inflammatory cytokines.[5]	**High-Dose vs. Low-Dose CQ:**[7] • A randomized, double-blind, Phase 2b study compared two different CQ regimens, CQ 600 mg twice daily for 10 days (high dose) versus CQ 450 mg twice daily for 1 day followed by 450 mg for 4 days (low dose), in hospitalized adults with suspected severe COVID-19 (respiratory rate >24 rpm, heart rate >125 bpm, oxygen saturation <90%, and/or shock). All patients received ceftriaxone plus AZM; 89.6% of patients received oseltamivir. Of note, both AZM and oseltamivir can increase the QTc interval. • The primary outcome for this analysis was mortality at 13 days after treatment initiation. The planned study sample size was 440 participants, which was sufficient to show a reduction in mortality by 50% with high-dose CQ. The study was stopped by the study's DSMB after 81 patients were enrolled. • *Results:* • 41 and 40 patients were randomized into the high-dose and low-dose CQ arms, respectively.

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date (Find clinical trials on ClinicalTrials.gov)

Chloroquine, continued			• The overall fatality rate was 27.2%.
			• Mortality by Day 13 was higher in the high-dose arm than in the low-dose arm (death occurred in 16 of 41 patients [39%] vs. in six of 40 patients [15%], respectively; *P* = 0.03). This difference was no longer significant when controlled by age (OR 2.8: 95% CI, 0.9–8.5).
			• Overall, QTcF >500 ms occurred more frequently among patients in the high-dose arm (18.9% of patients) than in the low-dose arm (11.1% of patients). Among those with confirmed COVID-19, QTcF >500 ms was also more frequent in the high-dose arm (24.1% of patients) than in the low-dose arm (3.6% of patients).
			• Two patients in the high-dose arm experienced ventricular tachycardia before death.
			• *Limitations:* More older patients and more patients with history of heart disease were randomized to the high-dose arm than to the low-dose arm.
			• *Interpretation:* Despite the small number of patients enrolled, this study raises concerns about an increased risk of mortality when high-dose CQ (600 mg twice daily) is administered in combination with AZM and oseltamivir.
			CQ vs. LPV/r:[8]
			• In a small randomized controlled trial in China, 22 hospitalized patients with COVID-19 (none critically ill) were randomized to receive oral CQ 500 mg twice daily or LPV/r 400 mg/100 mg twice daily for 10 days. Patients with a history of heart disease (chronic disease and a history of arrhythmia), or kidney, liver, or hematologic diseases were excluded from participation. The primary study outcome was SARS-CoV-2 PCR negativity at Days 10 and 14. Secondary outcomes included improvement of lung computed tomography scan at Days 10 and 14, discharge at Day 14, and clinical recovery at Day 10, as well as safety (which was determined by evaluating study drug-related AEs).
			• *Results:*
			  • Ten patients received CQ and 12 patients received LPV/r. At baseline, patients had good SpO_2 levels (97% to 98%).
			  • Compared to the LPV/r-treated patients, the CQ-treated patients had a shorter duration from symptom onset to initiation of treatment (2.5 days vs. 6.5 days, *P* < 0.001).

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date (Find clinical trials on ClinicalTrials.gov)
Chloroquine, continued			• Though not statistically significant, patients in the chloroquine arm were younger (median age 41.5 years vs. 53.0 years; *P* = 0.09). Few patients had co-morbidities. • At Day 10, 90% of the CQ-treated patients and 75% of the LPV/r-treated patients had a negative SARS-CoV-2 PCR test result. At Day 14, the percentages for the CQ-treated patients and the LPV/r-treated patients were 100% and 91.2%, respectively. • At Day 10, 20% of the CQ-treated patients and 8.3% of the LPV/r-treated patients had CT scan improvement. At Day 14, the percentages for the CQ-treated patients and the LPV/r-treated patients were 100% and 75%, respectively. • At Day 14, 100% of the CQ-treated patients and 50% of the LPV/r-treated patients were discharged from the hospital. • The risk ratios of these outcome data cross 1, and the results were not statistically significant. • Both drugs were generally well-tolerated. • *Limitations:* • The trial sample size was very small, and the participants were fairly young. • The CQ-treated patients were younger and had fewer symptoms prior to treatment initiation, which are variables that could have affected the study protocol-defined outcomes. • Patients who had chronic co-morbidities and who were critically ill were excluded from the study. • *Interpretation:* In this small randomized controlled trial, chloroquine and lopinavir/ritonavir showed similar efficacy in treating COVID-19.
Hydroxychloroquine	• Lupus erythematosus • Malaria • Rheumatoid arthritis[9]	• *In vitro* antiviral activity by increasing the pH of intracellular vacuoles and altering protein degradation pathways, thereby interfering with the virus/cell fusion and glycosylation of cellular receptors[4,5] • Immunomodulatory effects may lead to a reduction in pro-inflammatory cytokines.[5]	**Observational Study of HCQ at a Large Medical Center in New York City:[10]** • This observational study evaluated 1,376 consecutive adults with COVID-19 who were admitted to a large New York City hospital (after excluding 70 patients who died or who were transferred within 24 hours after presenting to the emergency department). The study assessed the time from study baseline (24 hours after patients arrived at the emergency department) to intubation or death based on whether the patient received HCQ at baseline or during follow-up. Patients who received HCQ were prescribed a twice-daily dose of HCQ 600 mg on the first day and 400 mg daily for 4 additional days; this was based on the clinical guidance of the hospital.

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date (Find clinical trials on ClinicalTrials.gov)
Hydroxychloroquine, continued			• *Results:* • 811 patients (58.5%) received HCQ and 565 (41.1%) did not. • Patients who received HCQ were older and more likely to have hypertension (49.1% vs. 6.7%) and to be on systemic steroids (26.6% vs. 10.1%) than those who did not receive HCQ. • Patients who received HCQ were more likely to receive concomitant AZM (59.9% vs. 22.5%) and/or other antibiotics (74.5% vs. 54.0%) than those who did not receive HCQ. • Patients who received HCQ had higher levels of inflammatory markers. • HCQ-treated patients had more severe hypoxia, with a lower PaO_2/FiO_2 ratio at baseline than patients who did not receive HCQ (median of 233 mm Hg vs. 360 mm Hg). • Most patients (85.9%) received HCQ within 48 hours of presentation. • 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). • There was also 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:* Despite the large size of this study, it suffers from the inherent limitations of an observational study. These include residual confounding from confounding variables that were unrecognized and/or unavailable for analysis. • *Interpretation:* The use of HCQ for treatment of COVID-19 was not associated with harm or benefit in a large observational study. **Retrospective Observational Cohort from the United States Veterans Health Administration** *This study has not been peer reviewed*[11] • An observational, retrospective cohort study analyzed data from patients with confirmed COVID-19 who were hospitalized at the United States Veterans Health Administration medical centers between March 9, 2020, and April 11, 2020. Patients were categorized as having received either HCQ, HCQ plus AZM, or no HCQ. Doses and duration of HCQ or AZM use were not specified. All patients also received standard supportive management for COVID-19. The primary endpoints were death and the

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date (Find clinical trials on ClinicalTrials.gov)
Hydroxychloroquine, continued			need for mechanical ventilation. Associations between treatment and outcomes were determined using propensity score adjustment, including demographic, co-morbid, and clinical data (including predictors of COVID-19 disease severity). Patients were included in the analysis if BMI, vital signs, and discharge disposition were noted in their medical records. • *Results:* • 368 patients were eligible for analysis. These patients were categorized into three treatment groups: HCQ (n = 97), HCQ plus AZM (n = 113), or no HCQ (n = 158). The median ages for the patients in each group were 70, 68, and 69 years, respectively. All patients were male. • 70 patients died; 35 of those who died (50%) were not receiving mechanical ventilation. • No difference was observed between the groups in the risk of mechanical ventilation. • Compared with the no HCQ group, the risk of death from any cause was higher in the HCQ group (adjusted HR 2.61; 95% CI, 1.10–6.17; $P = 0.03$), but not in the HCQ plus AZM group (adjusted HR 1.14; 95% CI, 0.56–2.32, $P = 0.72$). • There was no between-group difference in the risk of death after ventilation. • *Limitations:* • The patient population was entirely male. • The dose and duration of administration for HCQ and AZM were not included in the report. Patients were included if they received a single dose of either or both drugs. • Propensity score adjustment was used to account for differences between the groups, but the possibility of residual confounding cannot be excluded, as patients who were more ill may have been more likely to receive HCQ. • No imaging data were presented; severity of chest X-ray findings could predict worse outcomes. • The use of other antiviral or immune modulatory agents were not reported. • The reason for the high mortality among patients who did not receive mechanical ventilation is not clear, especially as most of these patients appear to have had mild/moderate disease at admission.

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date (Find clinical trials on ClinicalTrials.gov)
Hydroxychloroquine, continued			• *Interpretation:* This study showed no beneficial effect of HCQ plus AZM for the treatment of COVID-19 and a possible association between HCQ and increased mortality; however, residual confounding may have affected the study results. **Randomized, Controlled Trial of HCQ vs. SOC for Mild/Moderate COVID-19:**[12] • This multicenter, randomized, open-label trial compared HCQ 1,200 mg once daily for 3 days followed by HCQ 800 mg once daily for the rest of the treatment duration (2 weeks for patients with mild/moderate COVID-19 [99% of the patients] and 3 weeks for two patients with severe disease) versus SOC. • The primary outcome was negative PCR within 28 days. Secondary outcomes were alleviation of symptoms (resolution of fever, SpO_2 >94% on room air, resolution of respiratory symptoms), improvement in markers of inflammation (including CRP), and improvement of lung lesions on a chest X-ray within 28 days. • *Results:* • 75 patients were enrolled in each study arm. Patients were randomized at a mean of 16.6 days after symptom onset. • No difference was found between the HCQ arm and the SOC arm in negative PCR conversion rate within 28 days (85.4% of participants vs. 81.3% of participants, respectively) or in time to negative PCR conversion (median of 8 days vs. 7 days, respectively). • There was no difference in the probability of symptom alleviation between the groups in the intention-to-treat analysis. • AEs occurred in 30% of the participants in the HCQ arm (most commonly diarrhea) versus in 9% of the participants in the SOC arm. • *Limitations:* • It is unclear how the overall rate of symptom alleviation was calculated. • The duration of HCQ use (2 weeks) was longer than in most other observational cohort studies or clinical trials for the treatment of COVID-19. • The study did not reach the target sample size.

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date (Find clinical trials on ClinicalTrials.gov)
Hydroxychloroquine, continued			• *Interpretation:* This study demonstrated no difference in viral clearance between HCQ and SOC. **Observational Cohort of HCQ vs. No HCQ:**[13] • This observational, retrospective cohort study analyzed data for adult patients who were hospitalized for COVID-19 pneumonia at four French tertiary care centers over a 2-week period (March 17–31, 2020). Patients aged 18 to 80 years were eligible if they had PCR-confirmed SARS-CoV-2 infection and required oxygen by mask or nasal cannula. Exclusion criteria included HCQ initiation before hospitalization, receipt of another experimental COVID-19 treatment within 48 hours, organ failure that required immediate admission to the ICU or continuous care unit, admission with ARDS that required noninvasive ventilation with continuous positive airway pressure or mechanical ventilation, discharge from the ICU to standard care, or if a decision was made to limit or stop active treatments prescribed at admission. Patients in one treatment arm received a daily dose of HCQ 600 mg within 48 hours of admission; patients in the other arm did not receive HCQ during the same period. The decision to use HCQ to treat a patient was based on local medical consensus and prescriber opinion and was reportedly independent of patient characteristics. Patients were followed from baseline until death, loss to follow-up, or the end of the follow-up period on April 24, 2020. The primary outcome was survival without transfer to the ICU at Day 21. An inverse probability of treatment weighting approach was used to "emulate" randomization. • *Results:* • Of the 181 patients who were eligible for the analysis, 84 participants received HCQ within 48 hours, eight received HCQ beyond 48 hours, and 89 participants did not receive HCQ. • Co-morbidities were less common in the HCQ group; overall initial COVID-19 severity was well balanced across the treatment arms. • In the HCQ group, 18% of the patients received concomitant AZM and 52% of the patients received amoxicillin/clavulanic acid. • In the inverse probability of treatment weighted analysis, there was no difference in the primary outcome (survival rate without ICU transfer at Day 21) between the HCQ group (76% of participants) and the non-HCQ group (75% of participants). Similarly, there was no difference between the groups in the secondary outcomes of survival and survival without ARDS at Day 21.

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date (Find clinical trials on ClinicalTrials.gov)
Hydroxychloroquine, continued			• Among the 84 patients who received HCQ within 48 hours, eight patients (10%) experienced ECG changes requiring treatment discontinuation at a median of 4 days from the start of dosing, including seven patients with a QTc that prolonged >60 ms and one patient with new onset, first-degree AV block. None of these patients received AZM. • *Limitations:* This was a retrospective, nonrandomized study. • *Interpretation:* In this retrospective study, there was no difference in clinically important outcomes between patients who received HCQ within 48 hours of hospital admission and those who did not. **A Case Series of HCQ vs. Control:**[14] • In a case series from France, 26 hospitalized adults with SARS-CoV-2 infection categorized as asymptomatic or with upper or lower respiratory tract infection who received HCQ 200 mg three times daily for 10 days were compared to 16 control individuals (i.e., those who refused treatment, did not meet eligibility criteria, or were from a different clinic). • *Results:* • Six patients in the HCQ group were excluded from the analysis for the following reasons: • One patient died. • Three patients were transferred to the ICU. • One patient stopped the study drug due to nausea. • One patient withdrew from the study. • Six patients also received AZM. • By Day 6, NP PCRs were negative in 14 of 20 HCQ-treated patients (70%) and two of 16 controls (12.5%). • Among the HCQ patients, eight of 14 (57.1%) who received only HCQ and six of six (100%) who received HCQ and AZM had negative NP PCRs by Day 6. • Clinical outcomes were not reported for all patients. • *Limitations:* • The sample size of the series is small. • The criteria for enrollment of cases and controls is unclear. • Asymptomatic individuals were enrolled.

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date (Find clinical trials on ClinicalTrials.gov)
Hydroxychloroquine, continued			• Exclusion of six HCQ-treated patients includes one death and three ICU transfers. • No clinical outcomes were reported; thus, the clinical significance of a negative PCR is unknown. • The reason for the addition of AZM for some patients is unclear. • *Interpretation:* Methodologic problems with this case series limit the ability to draw conclusions regarding the efficacy of HCQ with or without AZM.
Hydroxychloroquine Plus Azithromycin	See the Azithromycin section above.	See the Azithromycin section above.	**Case Series of HCQ Plus AZM:**[15] • In a case series of 80 hospitalized patients with COVID-19 (including six patients from a previous study),[14] patients were treated with HCQ 200 mg three times daily for 10 days plus AZM 500 mg for 1 day followed by 250 mg once daily for 4 days. Mean time from symptom onset to treatment was about 5 days. The outcomes that were evaluated included the need for oxygen therapy or ICU transfer after ≥3 days of therapy, SARS-CoV-2 level by PCR, SARS-CoV-2 culture (in a subset of patients; a convenience sample), and length of stay in the infectious diseases ward. • *Clinical Results:* • One patient died (1.2%), three required ICU transfer (3.8%), and 12 required oxygen therapy (15%). • 65 patients (81.2%) were discharged to their homes or transferred to other units for continuing treatment; 14 patients (17.4%) remained hospitalized at the time the study results were published. • *Laboratory Results:* • NP SARS-CoV-2 PCR was negative in 83% of patients by Day 7 and in 93% of patients by Day 8. • In the subset of patients who had respiratory sample viral cultures performed at Day 5, results were negative for 97.5% of the samples. • *Limitations:* • The trial lacked a control group, which is particularly important because many people with mild disease improve in the absence of treatment. • The definition of "discharge" varied. • The lack of complete or longer-term follow-up.

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date (Find clinical trials on ClinicalTrials.gov)
Hydroxychloroquine Plus Azithromycin, continued			• *Interpretation:* The multiple issues with trial design and the lack of a comparison group limit the usefulness of this study to inform recommendations. **Small Prospective Case Series of HCQ Plus AZM:**[16] • A prospective case series from France assessed eleven consecutive hospitalized patients with COVID-19. • *Results:* • Eight of the 11 patients had significant co-morbid conditions: obesity (n = 2), solid cancer (n = 3), hematological cancer (n = 2), and HIV infection (n = 1). • Ten of 11 patients were receiving supplemental oxygen upon treatment initiation. • All patients were treated with HCQ 600 mg once daily for 10 days and AZM 500 mg once daily for 1 day followed by 250 mg once daily for 4 days. • Within 5 days, the condition of three patients worsened, including one patient who died and two patients who were transferred to the ICU. • AEs: HCQ was discontinued in one patient due to QTc prolongation. • Qualitative NP PCR remained positive at Days 5 and 6 after treatment initiation in eight of 10 patients. • *Limitations:* This is a case series that included a small number of patients. • *Interpretation:* In this small case series, most patients who received HCQ plus AZM did not have rapid viral clearance. **Case Series of Changes in QTc Interval in Patients Who Received HCQ Plus AZM:**[17] • A case series in the United States reported changes in QTc interval in 84 patients with COVID-19 who received the combination of HCQ (400 mg twice daily for 1 day, followed by 200 mg twice daily for 4 days) and AZM (500 mg once daily for 5 days). • *Results:* • 84 patients were enrolled; 74% were male, with a mean age of 63 ± 15 years. 65% had HTN, mean serum creatinine was 1.4 mg/dL at baseline, 13% required vasopressors, and 11% had CAD.

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date (Find clinical trials on ClinicalTrials.gov)
Hydroxychloroquine Plus Azithromycin, continued			• Concomitant drugs that may prolong QTc interval: 11% of participants on neuropsychiatric drugs and 8% of participants received levofloxacin, lopinavir/ritonavir, or tacrolimus. • Four patients died, without arrhythmia. • The mean baseline QTc was 435 ± 24 ms and the mean maximum QTc was 463 ± 32 ms. • The mean time to maximum QTc was 3.6 ± 1.6 days. ECG follow-up was done for a mean of 4.3 days. • Nine patients (11%) developed QTc >500 ms; the QTc increased by 40 to 60 ms and >60 ms in 18% and 12% of patients, respectively. • *Limitations:* • Case series, descriptive • *Interpretation:* This case series demonstrates that HCQ and AZM in combination can prolong QTc and that use of the combination warrants careful monitoring.
HIV Protease Inhibitors **Note:** LPV/r and DRV/c have been studied in patients with COVID-19.	• HIV Infection	• No data on *in vitro* activity of LPV/r against SARS-CoV-2 • Possible inhibition of SARS-CoV-2 protease 3CLpro[18] • *In vitro* data does not support the use of DRV/c for the treatment of COVID-19.[19]	**Randomized Controlled Trial of LPV/r vs. SOC:** In a clinical trial that randomized 199 patients to LPV/r 400 mg/100 mg PO twice daily for 14 days or to SOC, patients randomized to the LPV/r arm did not have a shorter time to clinical improvement. • *Results:* • There was a lower, but not statistically significant, mortality rate for the LPV/r group (19.2%) than for the SOC group (25.0%) and shorter ICU stay for those in the LPV/r group than in the SOC group (6 days vs. 11 days; difference = -5 days; 95% CI, -9 to 0). • The duration of hospital stays and time to clearance of viral RNA from respiratory tract samples did not differ between the LPV/r and SOC arms. • Nausea, vomiting, and diarrhea were all more frequent in the LPV/r-treated group. • The study was powered only to show a fairly large effect. • *Limitations:* • The study was not blinded, which may have affected the assessments of clinical improvement. • The study was underpowered to show small effects.

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date (Find clinical trials on ClinicalTrials.gov)
HIV Protease Inhibitors, continued			• *Interpretation:* A moderate-sized randomized trial failed to find a virologic or clinical benefit of LPV/r over SOC. **LPV/r vs. Arbidol vs. SOC[20]** *This study has not been peer reviewed.* • In a trial of 86 hospitalized patients with mild-to-moderate COVID-19, 34 patients were randomized to LPV/r, 35 patients to the broad-spectrum antiviral Arbidol (available in Russia), and 17 patients to SOC. • *Results (Comparison of LPV/r to SOC):* • The time to a negative SARS-CoV-2 nucleic acid pharyngeal swab was similar for patients receiving LPV/r (mean 9 days [SD 5.0]) and for those receiving SOC (mean 9.3 days [SD 5.2]). • Progression to severe/critical status occurred among eight (24%) patients receiving LPV/r and two patients (12%) on SOC. • *Limitations:* • The trial had a small sample size. • The effectiveness of Arbidol in treating COVID-19 is unknown. • *Interpretation:* The small sample size of this trial limits its usefulness. **LPV/r vs. CQ:** • A small randomized study in China compared LPV/r to CQ. Please refer to the CQ section for the study description.

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date (Find clinical trials on ClinicalTrials.gov)
Remdesivir (GS-5734)	• Not approved by FDA • Investigational antiviral agent	• Adenosine nucleotide analog prodrug that undergoes hydrolysis to its active form, which inhibits viral RNA-dependent RNA polymerase[21] • Potent *in vitro* activity demonstrated in SARS-CoV-2-infected Vero E6 cells[22] • In a rhesus macaque model of SARS-CoV-2 infection, animals who were started on RDV soon after inoculation had lower lung virus levels and less lung damage than control animals.[23]	**Multinational Randomized Controlled Trial of RDV Versus Placebo in Hospitalized Patients:[24]** • ACTT is an NIH-sponsored, multinational, randomized, double-blind placebo-controlled trial in hospitalized adults with COVID-19. Participants were randomized 1:1 to receive IV RDV or placebo for 10 days. The primary study endpoint was time to clinical recovery, which was defined as either discharge from the hospital or hospitalization for infection control purposes only. Severity of illness at baseline and at Day 15 was assessed using an ordinal scale: 1) Not hospitalized, no limitations 2) Not hospitalized, with limitations 3) Hospitalized, no active medical problems 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 • *Study Population:* The study population consisted of hospitalized patients aged ≥18 years with laboratory-confirmed SARS-CoV-2 infection. Patients were enrolled if they met at least one of the following conditions: • The patient had pulmonary infiltrates, as determined by radiographic imaging; • SpO_2 was ≤94% on ambient air; • The patient required supplemental oxygen; • The patients was on mechanical ventilation; *or* • The patient was on ECMO. • The study excluded individuals who had ALT or AST levels >5 times the ULN, those who had an eGFR <30 mL/min, and those who were pregnant or breastfeeding. • *Preliminary Results:* • Of 1,063 enrolled participants, 1,059 had preliminary results available for analysis (n = 538 for the RDV group; n = 521 for the placebo group).

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date (Find clinical trials on ClinicalTrials.gov)
Remdesivir, continued (GS-5734)			• The mean age was 58.9 years; 64.3% of participants were male, 53.2% were white, and 79.8% were enrolled in North America. • 52.1% of participants had two or more co-morbidities; 37% were obese (mean BMI 30.6 kg/m^2) • The median time from symptom onset to randomization was 9 days (IQR 6–12 days). • As of the time of the preliminary analysis, 391 RDV recipients and 340 placebo recipients had completed the study through Day 29, recovered, or died. • Eight RDV recipients and nine placebo recipients terminated the study prior to Day 29. • 132 RDV recipients and 169 placebo recipients had not recovered and had not completed the Day 29 follow-up visit at the time of this analysis. • RDV significantly reduced time to recovery compared to placebo (median time to recovery 11 days vs. 15 days, respectively; recovery rate ratio 1.32; 95% CI, 1.12–1.55; $P < 0.001$). • Clinical improvement based on the ordinal scale was significantly higher in patients who received RDV than in those who received placebo at Day 15 (OR 1.50; 95% CI, 1.18–1.91, $P < 0.001$). • The benefit of RDV on reducing time to recovery was clearest in the subgroup of hospitalized patients who required supplemental oxygenation at study enrollment (ordinal scale 5; n = 421). • Among patients who were on mechanical ventilation or ECMO at enrollment (ordinal scale 7; n = 272), there was no observed difference between the RDV and placebo groups in time to recovery (recovery rate ratio 0.95; 95% CI, 0.64–1.42). • Among patients classified as having mild to moderate disease at enrollment, there was no difference in the median time to recovery between the RDV and placebo groups (recovery rate ratio 1.09; 95% CI, 0.73–1.62; n = 119). Mild to moderate disease was defined as SpO_2 >94% and respiratory rate <24 bpm without supplemental oxygen. • The mortality estimate by Day 14 was lower in the RDV arm than in the placebo arm (7.1% vs. 11.9%, respectively), but the difference was not statistically significant (HR 0.70; 95% CI, 0.47–1.04).

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date (Find clinical trials on ClinicalTrials.gov)
Remdesivir, continued (GS-5734)			• The use of RDV was associated with shorter time to recovery regardless of duration of symptoms prior to randomization (≤10 days vs. >10 days). • The percentages of participants with serious AEs were similar in the RDV and placebo groups (21.1% vs. 27.0%, respectively). • Transaminase elevations occurred in 4.1% of RDV recipients and 5.9% of placebo recipients. • *Limitations:* At the time of publication, the full dataset was not available for analysis. • *Interpretation:* In patients with severe COVID-19, RDV reduced the time to clinical recovery. The benefit of RDV was most apparent in hospitalized patients who were not intubated but who required supplemental oxygen. There was no observed benefit of RDV in those who were mechanically ventilated, but the follow-up period may have been too short to see a difference between the RDV and placebo groups. There was no observed benefit of RDV in patients with mild or moderate COVID-19, but the number of participants in these categories was relatively small. **Multinational Randomized Trial of Different Durations of RDV Treatment in Hospitalized Patients:**[25] • This was a manufacturer-sponsored, multinational, randomized, open-label trial in hospitalized adolescents and adults with COVID-19. Participants were randomized 1:1 to receive either 5 days or 10 days of IV RDV. The primary study endpoint was clinical status at Day 14, which was assessed using a seven-point ordinal scale: 1) Death 2) Hospitalized, on invasive mechanical ventilation or ECMO 3) Hospitalized, on noninvasive ventilation or high-flow oxygen devices 4) Hospitalized, requiring low-flow supplemental oxygen 5) Hospitalized, not requiring supplemental oxygen, but requiring ongoing medical care for COVID-19 or for other reasons 6) Hospitalized, not requiring supplemental oxygen or ongoing medical care (other than the care that was specified in the protocol for RDV administration) 7) Not hospitalized

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date (Find clinical trials on ClinicalTrials.gov)
Remdesivir, continued (GS-5734)			• *Study Population:* The study enrolled hospitalized patients aged ≥12 years with RT-PCR-confirmed SARS-CoV-2 infection and radiographic evidence of pulmonary infiltrates. Patients in this study had either SpO_2 ≤94% on ambient air or were receiving supplemental oxygen. The study excluded patients who were receiving mechanical ventilation or ECMO or who had multiorgan failure, an ALT or AST level >5 times ULN, or an estimated creatinine clearance of <50 mL/min. Patients were also excluded if they had received an agent with putative anti-SARS-CoV-2 activity within 24 hours of starting treatment in the trial. • *Results:* • Of 402 randomized participants, 397 began 5 days (n = 200) or 10 days (n = 197) of RDV treatment. • In the 5-day group, the median age was 61 years; 60% of participants were male, and 71% were white. In the 10-day group, the median age was 62 years; 68% of participants were male, and 70% were white. The frequency of coexisting conditions was similar in both groups. • The median time from symptom onset to first dose of RDV was 8 days in the 5-day group and 9 days in the 10-day group. The median duration of hospitalization before the first RDV dose was 2 days in both groups. • At baseline, patients in the 10-day group had worse clinical status (based on the ordinal scale distribution) than those in the 5-day group (P = 0.02). • A few patients were on mechanical ventilation: four (2%) were assigned to the 5-day group, and nine (5%) were assigned to the 10-day group. Although mechanical ventilation was an exclusion criterion for enrollment, some patients were intubated between screening and treatment initiation; others were protocol deviations. • 172 participants (86%) in the 5-day group completed a median of 5 days of treatment, and 86 (44%) in the 10-day group completed a median 9 days of treatment. • 65% of patients in the 5-day group and 54% of those in the 10-day group had a two-point improvement in clinical status on the ordinal scale. • After adjusting for imbalances in the baseline clinical status, the Day 14 distribution in clinical status on the ordinal scale was similar in the 5-day and 10-day groups (P = 0.14)

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date (Find clinical trials on ClinicalTrials.gov)
Remdesivir, continued (GS-5734)			• The time to clinical improvement of at least two levels on the ordinal scale (median day of 50% cumulative incidence) was similar in the 5-day and 10-day groups (10 days vs. 11 days, respectively). • The median durations of hospitalization among patients who were discharged on or before Day 14 were similar in the 5-day group (7 days; IQR 6–10) and 10-day group (8 days; IQR 5–10). • By Day 14, 120 patients (60%) in the 5-day group had been discharged and 16 (8%) had died; in the 10-day group, 103 patients (52%) had been discharged and 21 (11%) had died. • Serious AEs were more common in the 10-day group (35%) than in the 5-day group (21%); 4% of patients in the 5-day group and 10% of patients in the 10-day group stopped treatment because of AEs. • *Limitations:* • This was an open-label trial without a placebo control group, so the clinical benefit of RDV could not be assessed. • There were baseline imbalances in the clinical statuses of participants in the 5-day and 10-day groups. At the start of the study, more patients in the 10-day group than in the 5-day group were receiving noninvasive ventilation or high-flow oxygen (30% vs. 24%, respectively), and fewer patients in the 10-day group than in the 5-day group were not receiving supplemental oxygen (11% vs. 17%, respectively). • *Interpretation:* In hospitalized patients with COVID-19 who were not on mechanical ventilation or ECMO, RDV treatment for 5 or 10 days had similar clinical benefit. Because this trial only evaluated a few patients who were on mechanical ventilation, the appropriate duration of RDV treatment for critically ill patients is still unclear. **Randomized Controlled Trial of RDV vs. Placebo for Severe COVID-19 in China:**[26] • This was a multicenter, double-blind, randomized, placebo-controlled trial that evaluated patients with severe COVID-19 in China. Patients were randomized 2:1 to receive IV RDV or normal saline placebo for 10 days. Concomitant use of LPV/r, corticosteroids, and interferons were allowed. The primary study endpoint was time to clinical improvement, defined as improvement on an ordinal scale or discharged alive from the hospital, whichever came first. The planned sample size was 453 patients.

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date (Find clinical trials on ClinicalTrials.gov)
Remdesivir, continued (GS-5734)			• The study enrolled hospitalized adults with laboratory-confirmed COVID-19 whose time from symptom onset to randomization was <12 days, whose O_2 saturation was ≤94% on room air or whose PaO_2/FiO_2 was <300 mmHg, and who had radiographically confirmed pneumonia. • *Results:* • Between February 6 and March 12, 2020, 237 hospitalized patients were enrolled and randomized to receive RDV (n = 158) or placebo (n = 79). The study was stopped before target enrollment was reached due to control of the COVID-19 outbreak in China. • The participants' median age was 65 years, and 56% of the participants in the RDV arm and 65% in the placebo arm were male. • There were more patients with HTN, DM, or CAD in the RDV arm than in the placebo arm. • At Day 1, 83% of the patients required supplemental oxygen by nasal cannula or mask; only one patient required mechanical ventilation or ECMO. • The median time from symptom onset to randomization was 9 days in the RDV group and 10 days in the placebo group. • 65% of the patients in the RDV group and 68% of patients in the placebo group received corticosteroids. • 28% of the participants in the RDV group and 29% of the participants in the placebo group received LPV/r. • 29% of participants in the RDV arm and 38% of participants in the placebo arm received interferon alfa-2b. • *Study Endpoints:* • There was no difference in the time to clinical improvement between the RDV and placebo groups (a median of 21 days vs. 23 days, respectively; 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 in the RDV arm than in the placebo arm (median of 18 days vs. 23 days, respectively; HR 1.52; 95% CI, 0.95–2.43); however, this was not statistically significant. • The 28-day mortality rate was similar for the two study arms: 14% of participants in RDV arm versus 13% in placebo arm.

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date (Find clinical trials on ClinicalTrials.gov)
Remdesivir, continued (GS-5734)			• There was no difference in SARS-CoV-2 viral load at baseline, and the rate of decline over time was similar between the two groups. • The number of participants who experienced AEs was similar between the two groups (66% in the RDV arm and 64% in the placebo arm). • More participants in the RDV arm discontinued therapy due to AEs (12% in RDV group vs. 5% in placebo group). • *Limitations:* • The study was terminated early; as a result, the sample size did not have sufficient power to detect differences in clinical outcomes. • The use of concomitant medications (corticosteroids, LPV/r, interferon) may have obscured the effects of RDV. • *Interpretation:* There was no difference in time to clinical improvement, 28-day mortality, or rate of viral clearance between RDV-treated and placebo-treated patients. **Uncontrolled Case Series from RDV Compassionate Use Program:** • In an uncontrolled case series of 53 hospitalized patients with COVID-19, most patients needed less oxygen support after receiving compassionate use RDV. There was no comparison group, however, so it is not possible to assess whether the improvement was the result of using RDV.[27]

Key: 3CLpro = 3-chymotrypsin-like protease; ACE2 = angiotensin-converting enzyme 2; ACTT = Adaptive COVID-19 Treatment Trial; AE = adverse effect or adverse event; ALT = alanine transaminase; ARDS = acute respiratory distress syndrome; AST = aspartate transaminase; AV = atrioventricular; AZM = azithromycin; BMI = body mass index; CAD = coronary artery disease; CI = confidence interval; CQ = chloroquine; CRP = C-reactive protein; CT = computerized tomography; DM = diabetes mellitus; DRV/c = darunavir/cobicistat; DSMB = data safety monitoring board; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; eGFR = glomerular filtration rate; FDA = Food and Drug Administration; HCQ = hydroxychloroquine; HIV = human immunodeficiency virus; HR = hazard ratio; HTN = hypertension; ICU = intensive care unit; IFN = interferon; IL = interleukin; IQR = interquartile range; IV = intravenous; LPV/r = lopinavir/ritonavir; NIH = National Institutes of Health; NP = nasopharyngeal; OR = odds ratio; PCR = polymerase chain reaction; PO = orally; QTcF = corrected QT interval by Fredericia; RDV = remdesivir; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SD = standard deviation; SOC = standard of care; STI = sexually transmitted infection; ULN = upper limit of normal

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Table 2b. Characteristics of Potential Antiviral Agents Under Evaluation for Treatment of COVID-19

(Last updated June 16, 2020)

- 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 from patients with COVID-19 where available.
- The effective dosing of these drugs for the treatment of COVID-19 is unknown. Therefore, the doses listed below are primarily derived from FDA-approved indications or from clinical trials investigating therapies for 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.
- Treatment-related AEs in patients with COVID-19 are not well defined; the validity of extrapolation between patient populations (i.e., FDA-approved use vs. COVID-19 use) is unknown, especially in critically ill patients. Reported AEs of these drugs that are associated with long-term therapy (i.e., months to years) are not included in this table because treatment for COVID-19 is not long term. 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 additional safety monitoring.
- The potential additive, antagonistic, or synergistic effects and the safety of 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 labeling, and visit the Liverpool COVID-19 Drug Interactions website.
- For information on drugs that prolong the QTc interval, please visit CredibleMeds.org.

Drug Name	Dosing Regimens *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.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Azithromycin (When Used with Hydroxychloroquine)	500 mg PO once on Day 1, then 250 mg PO daily on Days 2–5	• Gastrointestinal effects (e.g., diarrhea, nausea, vomiting) • Hepatotoxicity	• Baseline/follow-up ECG • Hepatic panel, SCr, potassium, magnesium	Additive effect with other drugs that prolong the QTc interval (including HCQ and CQ)	• The Panel **recommends against** the use of HCQ plus AZM for the treatment of COVID-19, except in a clinical trial **(AIII)**. • Half-life of up to 72 hours • A list of clinical trials is available here: Azithromycin

Drug Name	Dosing Regimens *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.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Chloroquine	**Dose Previously Suggested in an EUA for Adults and Adolescents Weighing ≥50 kg:** • 1 gm PO once on Day 1, then 500 mg PO once daily for 4–7 days of total treatment based on clinical evaluation.	• Prolonged QTc interval, Torsades de Pointes, AV block, ventricular arrhythmia • Gastrointestinal effects (e.g., nausea, vomiting, diarrhea, hepatitis) • Hypoglycemia • Hemolysis (especially in patients with G6PD deficiency) • Myopathy • Rash • Given the risk of heart rhythm problems, the FDA cautions against using CQ to treat COVID-19 outside of a hospital or a clinical trial.[1]	• CBC, hepatic panel, blood glucose, SCr, potassium, magnesium • Baseline/follow-up ECG if CQ is given with concomitant QTc-prolonging drugs or if the patient has underlying cardiac disease • Perform G6PD testing; CQ **is not recommended** in patients with G6PD deficiency. Consider using HCQ instead of CQ while awaiting G6PD test results.	• Additive effect with other drugs that prolong the QTc interval (including AZM) or that cause hypoglycemia • CYP2D6 inhibitor (moderate) • P-gp inhibitor	• The Panel **recommends against** the use of CQ for the treatment of COVID-19, except in a clinical trial **(AII)**. • The Panel **recommends against** using high-dose CQ (600 mg twice daily for 10 days) for the treatment of COVID-19 **(AI)**. • Dose-dependent toxicity • CQ is not commercially available in the United States • A list of clinical trials is available here: Chloroquine

Drug Name	Dosing Regimens *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.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Hydroxychloroquine	**Adults:** • Various loading and maintenance doses have been reported in studies or in clinical care. **Dose Previously Suggested in an EUA for Hospitalized Adults and Adolescents Weighing ≥50 kg:** • 800 mg PO once on Day 1, then 400 mg PO once daily for 4–7 days of total treatment based on clinical evaluation.	• Prolonged QTc interval, Torsades de Pointes, AV block, ventricular arrhythmia • Gastrointestinal effects (e.g., nausea, vomiting, diarrhea) • Hepatitis • Hypoglycemia • Myopathy • Anxiety, agitation, hallucinations, psychosis • Allergic reaction/rash • Given the risk of heart rhythm problems, the FDA cautions against the use of HCQ to treat COVID-19 outside of a hospital or a clinical trial.[1]	• CBC, hepatic panel, blood glucose, SCr, potassium, magnesium • Baseline ECG • Follow-up ECG if HCQ is given with concomitant QTc-prolonging drugs (e.g., AZM) or if the patient has underlying cardiac diseases	• Additive effect with other drugs that prolong the QTc interval (including AZM) or cause hypoglycemia • CYP2D6 inhibitor (moderate) • P-gp inhibitor	• The Panel **recommends against** HCQ for the treatment of COVID-19, except in a clinical trial **(AII)**. • The Panel **recommends against** the use of HCQ plus AZM for the treatment of COVID-19, except in a clinical trial **(AIII)**. • Available through EUA for hospitalized patients who cannot access HCQ via clinical trials. • Long elimination; half-life is 40–55 days. • Dose-dependent toxicity • A list of clinical trials is available here: Hydroxychloroquine

Drug Name	Dosing Regimens *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.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Lopinavir/Ritonavir	**Adults:** • LPV/r 400 mg/100 mg PO twice daily for 10–14 days **Neonates Aged ≥14 Days with a PMA ≥42 Weeks and Children Aged <18 Years:** • LPV 300 mg/m^2 plus RTV 75 mg/m^2 (maximum: LPV/r 400 mg/100 mg per dose) PO twice daily for a total of 7 days	• Nausea, vomiting, diarrhea • Transaminase elevation • QTc interval prolongation and Torsades de Pointes have been reported. • PR interval prolongation	• HIV antigen/antibody testing at baseline • Serum transaminase levels • Consider monitoring ECG when LPV/r is given with other QTc-prolonging medications.	**High Drug Interaction Potential** *Lopinavir:* • CYP3A4 inhibitor and substrate *Ritonavir:* • CYP3A4 > 2D6 substrate • Potent CYP3A4 and 2D6 inhibitor • Inducer of UGT1A1 and CYPs 1A2, 2C8, 2C9, and 2C19	• The Panel **recommends against** the use of LPV/r and other HIV PIs for the treatment of COVID-19, except in a clinical trial **(AI)**. • Liquid formulation is commercially available. Crushing LPV/r tablets may result in significantly decreased drug exposure (AUC ↓ 45%).[2] • Use with caution in patients with hepatic impairment. • A list of clinical trials is available here: Lopinavir/Ritonavir
Remdesivir *Investigational drug. Remdesivir is not approved by the FDA; however, it is available through an EUA,[a] a clinical trial, or the manufacturer's emergency access program.*	**In Patients Who Are Participating in Clinical Trials:** • Dose according to clinical trial protocol. **Panel's Recommendations for Adult and Pediatric Patients Weighing >40 kg** *For Patients with Severe COVID-19 Who Are Not Intubated:* • RDV 200 mg IV over 30–120 minutes for one dose, followed by RDV 100 mg IV on Day 2 through Day 5 **(AI)**. *For Mechanically Ventilated Patients, Patients on ECMO, and Patients Who Have Not Shown Adequate Improvement After 5 Days of Therapy:* • There are insufficient data on the optimal duration of therapy for mechanically ventilated patients, patients on ECMO, and	• Transient elevations in ALT or AST levels (Grade 1 or 2), typically after multiple days of therapy[3] • Mild, reversible PT prolongation without INR change or hepatic effects[3] • Drug vehicle is SBECD, which has been associated with renal toxicity. Potential for SBECD accumulation in patients with moderate to severe renal impairment • Gastrointestinal symptoms (e.g., nausea, vomiting)	• Monitor for infusion reactions. • Renal and hepatic function • **Do not administer** RDV if eGFR <30 mL/min (or if patient is receiving dialysis) or if ALT or AST level is >5 times ULN	• RDV levels are unlikely to be markedly altered by CYP2C8, CYP2D6, or CYP3A4 enzymes, or by P-gp or OATP drug transporters. RDV may be administered with weak to moderate inducers or with strong inhibitors of CYP450, OATP or P-gp.	**For Patients with Severe COVID-19:** • The Panel recommends RDV for treatment of COVID-19 in hospitalized patients with SpO_2 ≤94% on ambient air (at sea level) or those who require supplemental oxygen **(AI)**, and in patients who are on mechanical ventilation or ECMO **(BI)**. **For Patients with Mild to Moderate COVID-19:** • There are insufficient data to recommend for or against RDV for the treatment of patients with mild or moderate COVID-19.

Drug Name	Dosing Regimens *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.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Remdesivir, continued	patients who have not shown adequate improvement after 5 days of therapy. Some experts extend the total RDV treatment duration to up to 10 days **(CIII)**. **Note:** The EUA recommends 10-day therapy for patients on mechanical ventilation or ECMO. **Suggested Dose in EUA[b] for Pediatric Patients Weighing 3.5 to <40 kg** *Requiring Invasive Mechanical Ventilation and/or ECMO:* • RDV 5 mg/kg mg IV over 30–120 minutes for one dose on Day 1, followed by RDV 2.5 mg/kg IV daily over 30–120 minutes on Day 2 through Day 10 *Not Requiring Invasive Mechanical Ventilation and/or ECMO:* • RDV 5 mg/kg mg IV over 30–120 minutes for one dose on Day 1, followed by RDV 2.5 mg/kg IV daily over 30–120 minutes on Day 2 through Day 5. If no clinical improvement, may extend treatment for up to 5 additional days (for a total treatment duration of 10 days)			• Strong induction of P-gp is expected to modestly reduce RDV levels. The clinical relevance of lower RDV levels is unknown. The use of RDV with known inducers of P-gp (e.g., rifampin) **is not recommended**.	**Availability:** • RDV is available through an EUA[b] for the treatment of hospitalized adults and children with severe COVID-19. • RDV is also available for other patient populations through expanded access and compassionate use programs. • A list of clinical trials is available here: Remdesivir

[a] The FDA EUA permits the emergency use of the investigational product RDV for the treatment of suspected COVID-19 or laboratory-confirmed COVID-19 in adults and children who have been hospitalized with severe disease. Severe disease is defined as COVID-19 in patients with SpO_2 ≤94% on ambient air (at sea level) or in patients who require supplemental oxygen, mechanical ventilation, or ECMO.

Key: AE = adverse effect; ALT = alanine transaminase; AST = aspartate aminotransferase; AUC = area under the curve; AV = atrioventricular; AZM = azithromycin; CBC = complete blood count; CQ = chloroquine; CYP = cytochrome P; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; G6PD = glucose-6-phosphate dehydrogenase; GFR = glomerular filtration rate; HCQ = hydroxychloroquine; HIV = human immunodeficiency virus; INR = international normalized ratio; IV = intravenous; LPV = lopinavir; LPV/r = lopinavir/ritonavir; OATP = organic anion transporter polypeptide; P-gp = P-glycoprotein; PI = protease inhibitors; PMA = postmenstrual age; PO = orally; PT = prothrombin time; RDV = remdesivir; RTV = ritonavir; SBECD = sulfobutylether beta-cyclodextrin sodium; SCr = serum creatinine; UGT = uridine diphosphate glucuronyl transferase; ULN = upper limit of normal

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Immune-Based Therapy Under Evaluation for Treatment of COVID-19

(Last updated May 12, 2020)

Summary Recommendations

There are no Food and Drug Administration-approved drugs for the treatment of COVID-19. Although reports have appeared in the medical literature and the lay press have claimed that patients with COVID-19 have been successfully treated with a variety of agents, definitive clinical trial data are needed to identify safe and effective treatments for this disease. Recommended clinical management of patients with COVID-19 includes infection prevention and control measures and supportive care, including supplemental oxygen and mechanical ventilatory support when indicated. As in the management of any disease, treatment decisions ultimately reside with the patient and their health care provider.
Immune-Based Therapy:
• There are insufficient data to recommend either for or against the use of **COVID-19 convalescent plasma** or **SARS-CoV-2 immune globulins** for the treatment of COVID-19 **(AIII)**.
• The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of **non-SARS-CoV-2-specific intravenous immune globulin (IVIG)** for the treatment of COVID-19, except in the context of a clinical trial **(AIII)**. This 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.
• There are insufficient data to recommend either for or against the use of the following agents for the treatment of COVID-19 **(AIII)**:
  • **Interleukin-1 inhibitors** (e.g., **anakinra**)
  • **Interleukin-6 inhibitors** (e.g., **sarilumab**, **siltuximab**, **tocilizumab**)
• Except in the context of a clinical trial, the Panel **recommends against** the use of other immunomodulators, such as:
  • **Interferons (AIII)**, because of the lack of efficacy in treatment of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) and toxicity.
  • **Janus kinase inhibitors** (e.g., **baricitinib**) **(AIII)**, because of their broad immunosuppressive effect.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional **Rating of Evidence:** I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion

Several immune-based therapies that are directed at modifying the course of COVID-19 are currently under investigation or are being used off-label. These agents may target the virus (e.g., convalescent plasma) or modulate the immune response (e.g., interleukin-1 [IL-1] or interleukin-6 [IL-6] inhibitors).

For more information on host modifiers and immunotherapy that are under evaluation for COVID-19, see Tables 3a and 3b.

Interleukin-1 and Interleukin-6 Inhibitors and Other Immunomodulators

The cytokine profiles of serum from some patients with moderate to severe COVID-19 overlap with those seen in macrophage activation syndrome (MAS) and secondary hemophagocytic lymphohistiocytosis (sHLH).[1] MAS is characterized by hyperinflammation and manifests as fever, elevated ferritin levels, and pulmonary involvement, with a spectrum of presentation that includes sHLH.[2] Viruses are known triggers of MAS/sHLH, and high ferritin levels are associated with both MAS and mortality in patients with COVID-19.[3,4] Endogenous IL-1, a proinflammatory cytokine, potently induces IL-6 in monocytes and macrophages and is elevated in patients with COVID-19, MAS, and other conditions, such as severe chimeric antigen receptor T cell-mediated cytokine release syndrome.[5] The Janus kinase (JAK) family of enzymes regulate signal transduction in immune cells, and JAK inhibitors play a major role in inhibiting

and blocking cytokine release. IL-6 and IL-1 blockades and JAK inhibition, both of which have been proposed as an approach to treat the systemic inflammation associated with severe COVID-19 illness,[6] are reviewed in their respective pages.

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Convalescent Plasma and Immune Globulins

(Last updated May 12, 2020)

Recommendation:

- There are insufficient data to recommend either for or against the use of **COVID-19 convalescent plasma** or **SARS-CoV-2 immune globulins** for the treatment of COVID-19 **(AIII)**.

Rationale for Recommendation

Although convalescent plasma and virus-specific immune globulin have been used for other viral infections, sufficient clinical data are lacking for COVID-19, and potential risks include transfusion reactions. Theoretical risks include antibody-dependent enhancement of infection.

Rationale for Use in Patients with COVID-19

Plasma donated from individuals who have recovered from COVID-19 includes antibodies to SARS-CoV-2,[1] and SARS-CoV-2 immune globulin is a concentrated antibody preparation derived from the plasma of people who have recovered from COVID-19. Both products may help suppress the virus and modify the inflammatory response.

Clinical Data for COVID-19

Data supporting the use of convalescent plasma for COVID-19 are limited to a small retrospective cohort study, small case series, and case reports.[1-6] There are no clinical data on the use of SARS-CoV-2 immune globulin or hyperimmune globulin in patients with COVID-19.

Clinical Data for Other Viral Infections

The use of convalescent plasma has been evaluated for other viral diseases, such as severe acute respiratory syndrome (SARS), with some suggestion of potential benefit.[7-9] However, no convalescent blood products are currently licensed by the Food and Drug Administration (FDA).

There are no clinical data on the use of specific immune globulin or hyperimmune globulin products in patients with SARS or Middle East respiratory syndrome (MERS).

Several virus-specific immune globulin products are licensed for preventing post-transplant cytomegalovirus (CMV) disease (CytoGam) and post-exposure prophylaxis of varicella in high-risk individuals (VariZig).

Clinical Trials and Access

Randomized clinical trials to evaluate convalescent plasma for the treatment of COVID-19 are underway; a list is available at *ClinicalTrials.gov*. Trials evaluating SARS-CoV-2 immune globulins are in development.

The FDA has provided guidance for the use of COVID-19 convalescent plasma under an Emergency Investigational New Drug Application. The FDA has also approved a national expanded access program for the use of convalescent plasma for the treatment of patients with COVID-19. Clinicians can refer to the National COVID-19 Convalescent Plasma Project website for more information. People who have been fully recovered from COVID-19 for at least two weeks and who are interested in donating plasma can contact their local blood donor or plasma collection center or refer to the American Red Cross website.

Adverse Effects

The risks associated with plasma transfusion include antibody-mediated enhancement of infection, transfusion-associated acute lung injury, transfusion-associated circulatory overload, and allergic transfusion reactions.[3,10] Rare complications include the transmission of infectious pathogens and red cell alloimmunization.

Considerations in Pregnancy

Pathogen-specific immune globulins 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

Hyperimmune globulin has been used to treat several viral infections in children, including VZV, respiratory syncytial virus, and CMV; efficacy data for other respiratory viruses is limited. The efficacy and adverse effects associated with administration of convalescent plasma have not been well established.

Non-SARS-CoV-2-Specific Intravenous Immune Globulin

Recommendation:

- The COVID-19 Treatment Guidelines Panel **recommends against** the use of **non-SARS-CoV-2-specific intravenous immune globulin (IVIG)** for the treatment of COVID-19, except in the context of a clinical trial **(AIII)**. This 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.

Rationale for Recommendation

Currently, only a small proportion of the U.S. population has been infected with SARS-CoV-2. Therefore, products derived from the plasma of donors who were not confirmed to have had SARS-CoV-2 infection are not likely to contain SARS-CoV-2 antibodies.

Clinical Data for COVID-19

These data have not been peer reviewed.

In a retrospective, non-randomized cohort study of IVIG in eight treatment centers in China between December 2019 and March 2020, the authors found no difference in 28-day or 60-day mortality between the 174 patients who were treated with IVIG and the 151 patients who were not treated with IVIG.[1] Patients who received IVIG were hospitalized for a longer period (median of 24 days vs. 16 days) and experienced longer duration of disease (median of 31 days vs. 23 days). It should be noted that a higher proportion of IVIG-treated patients had severe disease at study entry (71 patients [41%] with critical status in the IVIG group vs. 32 [21%] in the non-IVIG group). A subgroup analysis that was limited to the critical 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 IVIG or no IVIG, and the IVIG group was older, was more likely to have coronary heart disease, and had a higher proportion of patients with severe COVID-19 disease at study entry. Patients also received numerous other concomitant therapies for COVID-19.

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Interleukin-1 Inhibitors

(Last updated June 11, 2020)

Recommendation

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

Rationale

There are no data from clinical trials on the use of IL-1 inhibitors in patients with COVID-19.

Anakinra is a recombinant human IL-1 receptor antagonist. It is approved 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. There are case reports and series that describe a favorable response with anakinra in these syndromes, including survival benefit in sepsis and reversing cytokine storm in adults with MAS after tocilizumab failure.[2,3]

Clinical Data for COVID-19

- A single-center case series reported outcomes following the open-label use of anakinra in nine hospitalized patients with COVID-19 who presented with 4 to 12 days of symptoms, required oxygen ≤6 liters/minute, and had serum C-reactive protein (CRP) ≥50 mg/L. Anakinra 100 mg was administered subcutaneously (SQ) every 12 hours for 3 days followed by 100 mg daily for up to 7 more days. Two of the nine patients also received hydroxychloroquine plus azithromycin; the other seven patients received no specific treatments. Anakinra was discontinued in one patient who progressed to acute respiratory failure after receiving the first dose of the drug. Data regarding the other eight patients indicated good clinical outcomes as assessed by oxygen flow, decline in CRP levels, and serial computerized tomography (CT) scans that showed no progression in infiltrates. By Day 11, none of the patients had died. Three patients experienced liver transaminase levels ≥3 times the upper limit of normal. However, the study results are difficult to interpret because of the low number of patients included in the case series and the absence of a comparison group.[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 center in Italy. All patients had COVID-19, moderate to severe acute respiratory distress syndrome (ARDS) that required non-invasive ventilation, and evidence of hyperinflammation (CRP ≥100 mg/L and/or ferritin ≥900 ng/mL). High-dose intravenous (IV) anakinra 5 mg/kg twice daily (the IV formulation is not approved in the United States) 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. Both the anakinra and control (standard treatment) 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 in the anakinra group than in the control group (90% vs. 56%, $P = 0.009$). However, the median age in the anakinra group was younger than in the control

group (median 62 years vs. 70 years), and a smaller percentage of 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]

Clinical Trials

A number of clinical trials for the treatment of COVID-19 are currently underway (a list of clinical trials is available here: Anakinra.

Adverse Effects

Anakinra was not associated with any significant safety concerns in trials of sepsis.[6-8] Increased rates of infection were reported with prolonged use in combination with tumor necrosis factor-alfa blockade, but not with short-term use.[9]

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.[10]

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 approved only in an SQ formulation.

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Interleukin-6 Inhibitors

(Last updated June 11, 2020)

Recommendation

- There are insufficient data to recommend either for or against the use of **interleukin-6 (IL-6) inhibitors** (e.g., **sarilumab**, **siltuximab**, **tocilizumab**) for the treatment of COVID-19.

Rationale

There are insufficient data from clinical trials on the use of IL-6 inhibitors in patients with COVID-19.

Rationale for Use in Patients with COVID-19

IL-6 is a pleiotropic, pro-inflammatory cytokine produced by a variety of cell types, including lymphocytes, monocytes, and fibroblasts. Infection by the related SARS-associated coronavirus induces a dose-dependent production of IL-6 from bronchial epithelial cells.[1] Elevations in IL-6 levels may be an important mediator when severe systemic inflammatory responses occur in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. COVID-19-associated systemic inflammation and hypoxic respiratory failure is associated with heightened cytokine release, as indicated by elevated blood levels of IL-6, C-reactive protein (CRP), D-dimer, and ferritin.[2-4]

Sarilumab

Sarilumab is a recombinant humanized anti-interleukin-6 receptor (IL-6R) monoclonal antibody that is approved by the Food and Drug Administration (FDA) for use in patients with rheumatoid arthritis. It is available as a subcutaneous (SQ) formulation and is not approved for cytokine release syndrome (CRS). A placebo-controlled clinical trial is evaluating the use of an intravenous (IV) formulation administered as a single dose for COVID-19.

Clinical Data for COVID-19

Press Release, April 27, 2020: In a Phase 2/3 clinical trial (*ClinicalTrials.gov* identifier NCT04315298), hospitalized COVID-19 patients were randomized (2:2:1) to receive sarilumab 400 mg, sarilumab 200 mg, or placebo. Preliminary data were released after an Independent Data Monitoring Committee recommended discontinuing the 200-mg arm and restricting future enrollment to critical patients only. At the time of the interim review of the first 457 participants enrolled, 145 were randomized to receive sarilumab 400 mg, 136 to receive sarilumab 200 mg, and 77 to receive placebo. At study entry, 28% of the patients had severe illness, 49% had critical illness, and 23% had multisystem organ dysfunction.[5]

Sarilumab decreased CRP, which changed by -79%, -77%, and -21% in the sarilumab 400 mg group, sarilumab 200 mg group, and placebo group, respectively (this is the primary outcome measure of the Phase 2 trial).

At the time of data analysis, the percentage of patients with critical illness (n = 226) who died or were on a ventilator was lower in the sarilumab 400 mg group (28%) than in the sarilumab 200 mg group (46%) and in the placebo group (55%). Comparing mortality alone, the percentage of patients who died also was lower in the sarilumab 400 mg group (23%) than in the sarilumab 200 mg group (36%) and in the placebo group (27%). In contrast to the positive trend in outcomes among patients with critical illness who received sarilumab, the April 27, 2020, press release about the study cited "negative trends" for most outcomes in patients with severe illness who received the drug.

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., tuberculosis [TB], other bacterial pathogens) have been reported only in the context of long-term use of sarilumab.

Considerations in Pregnancy

There are insufficient data to determine whether there is a drug-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.

Drug Availability

The SQ formulation of sarilumab is not approved for 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. A list of current clinical trials is available at *ClinicalTrials.gov*.

Siltuximab

Siltuximab is a recombinant human-mouse chimeric monoclonal antibody that binds IL-6 and that is approved by the FDA for use in patients with Castleman's disease. Siltuximab prevents the binding of IL-6 to both soluble and membrane-bound IL-6R, inhibiting IL-6 signaling. Siltuximab is dosed as an IV infusion.

Clinical Data in COVID-19

There are limited, unpublished data describing the efficacy of siltuximab in patients with COVID-19.[6] 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.

Clinical Trials

See *ClinicalTrials.gov* for a list of current clinical trials for siltuximab and COVID-19.

Adverse Effects

The primary adverse effects (AEs) reported for siltuximab have been related to rash. Additional AEs, such as serious bacterial infections, have been reported only in the context of long-term dosing of siltuximab once every 3 weeks.

Considerations in Pregnancy

There are insufficient data to determine whether there is a drug-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 utero* in the exposed fetus.

Drug Availability

Procuring siltuximab may be a challenge at some hospitals in the United States.

Tocilizumab

Tocilizumab is a recombinant humanized anti-IL-6R monoclonal antibody that is approved by the FDA for use in patients with rheumatologic disorders and CRS induced by chimeric antigen receptor T cell (CAR-T) therapy. Tocilizumab can be dosed for IV or SQ injection. For CRS, the IV formulation should be used.[7]

Clinical Data for COVID-19

- *Press Release, April 27, 2020:* The CORIMUNO-TOCI trial (*ClinicalTrials.gov* identifier NCT04331808) is an open-label, randomized trial of hospitalized patients with COVID-19 (n = 129 at seven sites in France) who had moderate or severe disease at study entry and who were randomized to receive tocilizumab plus standard of care (n = 65) or standard of care alone (n = 64). Patients received tocilizumab 8 mg/kg on Day 1. If there was no response to the treatment (i.e., no decrease in oxygen requirement), a second infusion of tocilizumab was administered on Day 3. In this preliminary report, the proportion of participants who had died or who needed ventilation (noninvasive or mechanical) was lower in the tocilizumab group than in the standard of care group. Detailed results of the trial have not been reported. The Data and Safety Monitoring Board resigned after the press release was issued.[8]
- *Published study:* Sixty-three hospitalized adult patients with COVID-19 were enrolled in a prospective, open-label study of tocilizumab for severe COVID-19. Criteria for inclusion in the study were polymerase chain reaction-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection; pulmonary involvement, assessed either by oxygen saturation ($Sa0_2$) <93% on room air or PaO_2/FiO_2 ratio <300 mm Hg; and at least three of the following: CRP >10 times normal values, ferritin >1,000 ng/mL, D-dimer >10 times normal values, or lactate dehydrogenase >2 times the upper level of normal. The patients' mean age was 62.6 years and most (88%) were male; 39.7% of the patients were febrile, and 95.7% had bilateral pulmonary infiltrates. Five patients were on mechanical ventilation at baseline. All of the patients received off-label antiretroviral protease inhibitors. Patients received either tocilizumab IV (8 mg/kg) or tocilizumab SQ (324 mg); within 24 hours after this initial dose, a second dose was administered to 52 of the 63 patients. Following administration of tocilizumab, fevers resolved in all but one patient, and CRP, ferritin, and D-dimer levels declined. The mean PaO_2/FiO_2 ratio of the patients increased between admission (152 +/- 53 mm Hg) and Day 7 of hospitalization (284 +/- 116 mm Hg). No moderate or severe adverse events attributable to tocilizumab were reported. The overall mortality rate was 11% (7 of 63 patients). No details were provided regarding the rate of secondary infections after tocilizumab use. The authors report an association between earlier use of tocilizumab and reduced mortality; however, interpretation of this result is limited because the study results did not describe a comparison group or specify an a priori comparison.[9]

Clinical Trials

See *ClinicalTrials.gov* for ongoing trials that are evaluating the use of tocilizumab for the treatment of COVID-19.

Adverse Effects

The primary laboratory abnormalities reported with tocilizumab treatment are elevated liver enzyme levels that appear to be dose dependent. Neutropenia or thrombocytopenia are uncommon. Additional AEs, such as risk for serious infections (e.g., TB, other bacterial pathogens), have been reported only in the context of continuous dosing of tocilizumab.

Considerations in Pregnancy

There are insufficient data to determine whether there is a drug-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

In children, tocilizumab is frequently used for CRS following CAR-T therapy[10] and it is occasionally used for MAS.[11] Pediatric data for its use in ARDS/sepsis are limited.

Drug Availability

Procuring IV tocilizumab may be a challenge at some hospitals in the United States.

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Other Immunomodulators

(Last updated May 12, 2020)

Interferons (Alfa, Beta)

Recommendation:

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

Rationale for Recommendation

Studies have shown that there was no benefit when interferons were used in patients with other coronavirus infections (i.e., severe acute respiratory syndrome [SARS], Middle East respiratory syndrome [MERS]), and the significant toxicities of interferons outweigh the potential for benefit. In addition, there is a lack of clinical trial results for patients with COVID-19.

Rationale for Use in Patients with COVID-19

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

Clinical Data for COVID-19

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.[1-5]

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

A randomized clinical trial that included 301 patients with acute respiratory distress syndrome[6] found that, compared to placebo, intravenous interferon beta-1a had no benefit as measured by ventilator-free days over a 28-day period (median of 10.0 days vs. 8.5 days) or mortality (26.4% vs. 23.0%).

Interferon-alfa-1b, which is not available in the United States, has been used in patients with COVID-19 in China, but it has been primarily used by atomization inhalation, and the clinical data have not yet been presented.

Adverse Effects

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

Drug-Drug Interactions

The most serious interactions with interferons are the potential for added toxicity with other immunomodulators and chemotherapeutic agents.

Considerations in Pregnancy

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), and exposure did not influence birth weight, height, or head circumference.

Considerations in Children

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

Janus Kinase Inhibitors (e.g., Baricitinib)

Recommendation:

- The Panel **recommends against** the use of **Janus kinase (JAK) inhibitors** (e.g., **baricitinib**) for the treatment of COVID-19, except in the context of a clinical trial **(AIII)**.

Rationale for Recommendation

At present, the broad immunosuppressive effect of JAK inhibitors outweighs the potential for benefit.

Baricitinib is an oral JAK inhibitor that works by inhibiting the JAK signal transducer and activator of transcription pathway. Baricitinib is approved by the Food and Drug Administration to treat rheumatoid arthritis and can ameliorate the chronic inflammation seen in interferonopathies.[7-9]

Rationale for Use in Patients with COVID-19

Baricitinib is a potent anti-inflammatory with activity against interferon-associated inflammation. It has also been postulated to have an antiviral effect. A related drug, ibrutinib, has been shown to decrease lung inflammation in a mouse model of influenza.[10,11]

Clinical Data for COVID-19

No clinical data has been reported to date.

Adverse Effects

Side effects have been observed with prolonged use, including upper respiratory infections (>10% of patients), increased levels of low-density lipoproteins, herpesvirus infections, increased liver function test levels, and thrombocytosis.

Considerations in Pregnancy

In animal studies of embryo-fetal development, there was increased embryo lethality in some species that were given baricitinib at very high doses, well above the recommended dose for humans.[12] The limited human data on the use of baricitinib are insufficient to evaluate the drug-associated risk for major birth defects or miscarriage.[12]

Corticosteroids

The role of corticosteroids as concomitant therapy in persons with COVID-19 is discussed in Considerations for Certain Concomitant Medications in Patients with COVID-19.

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Table 3a. Immune-Based Therapy Under Evaluation for Treatment of COVID-19: Clinical Data to Date

(Last updated June 11, 2020)

Information presented in this table may include data from pre-print/non-peer reviewed articles. This table will be updated as new information becomes available.

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
Blood Products			
COVID-19 Convalescent Plasma and SARS-CoV-2 Immune Globulins	Not approved by the FDA	Plasma donated from individuals who have recovered from COVID-19 includes antibodies to SARS-CoV-2.[1] Similarly, SARS-CoV-2 immune globulin is a concentrated antibody preparation derived from the plasma of people who have recovered from COVID-19. Both products may help suppress the virus and modify the inflammatory response.	**For COVID-19:** • Data supporting the use of convalescent plasma for COVID-19 are limited to a small retrospective cohort study, small case series, and case reports. • There are no clinical data on the use of SARS-CoV-2 immune globulin or hyperimmune globulin in COVID-19. **For Other Viruses:** • The use of convalescent plasma has been evaluated in other viral diseases (e.g., SARS), with some suggestion of potential benefit.[2-9] No convalescent blood products are currently licensed by the FDA. • There are no clinical data on the use of specific immune globulin or hyperimmune globulin in patients with SARS or MERS.
Non-SARS-CoV-2 Specific Intravenous Immune Globulin	• Primary immune disorders • Thrombocytopenic purpura • Kawasaki disease • Motor neuropathy • Prophylaxis of various bacterial and viral infections	• Passive immunity; human immunoglobulin is derived from pooled plasma of blood donors and contains antibodies against a broad spectrum of pathogens. • Currently, only a small proportion of the U.S. population has been infected with SARS-CoV-2. Therefore, products derived from the plasma of donors who were not confirmed to have had SARS-CoV-2 infection are not likely to contain SARS-CoV-2 antibodies.	**For COVID-19** • *Not Peer Reviewed:* A retrospective, nonrandomized cohort study of IVIG in eight treatment centers in China between December 2019 and March 2020 found no difference in 28-day or 60-day mortality between the 174 patients who were treated with IVIG and the 151 patients who were not treated with IVIG. Patients who received IVIG were hospitalized for longer (median of 24 days vs. 16 days) and experienced longer duration of disease (median of 31 days vs. 23 days). It should be noted that a higher proportion of IVIG-treated patients had severe disease at study entry (71 [41%] with critical status in the IVIG group vs. 32 [21%] in the non-IVIG group). A subgroup analysis that was limited to the critical patients suggested a mortality benefit at 28 days, which was no longer significant at 60 days. The results are difficult to interpret because of important limitations in the study design. In particular, patients were not randomized to receive IVIG versus no IVIG, and in the IVIG group, the patients were older and more likely to have coronary heart disease, and at study entry, the proportion of patients with severe COVID-19 disease was higher. Also, patients received numerous other concomitant therapies for COVID-19.[10]

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
Interferon Alfa and Interferon Beta			
Interferon Alfa and Interferon Beta	• IFN alfa-2b: Leukemia, melanoma, lymphoma, condylomata acuminata, Kaposi sarcoma, hepatitis B, hepatitis C • IFN alfa-1b is not available in the United States	• Elicits antiviral, antiproliferative, and immunomodulatory activities on numerous cell types[11-13]	No clinical data for COVID-19. **For MERS:**[14-17] • Retrospective studies with IFN alfa-2a, IFN alfa-2b, or IFN beta-1a in combination with ribavirin showed no clear benefit. • Ribavirin plus IFN alfa-2a survival rates: 30% to 100% in three small studies (n < 20)[18] • Ribavirin plus IFN alfa-2a or IFN alfa-2b: No significant improvement in clinical outcome or survival at 28 days.[19] • Ribavirin plus IFN beta-1a SQ: Retrospective analyses showed no significant effect on clinical outcome.[14] **Inhaled IFN beta-1a (SNG001):** • Phase 2 clinical trials showed improved lung function in asthma patients with respiratory infections.[20]
	• Multiple sclerosis (IFN beta-1a, IFN beta-1b)	• Elicits antiviral, antiproliferative, and immunomodulatory activities on numerous cell types (T cell, B cell, and cytokine function)[11,21] • Among IFN subtypes, IFN beta-1b shows greatest *in vitro* inhibition of MERS-CoV.[16,22] • *In vitro* activity against MERS-CoV in lung cells.[20]	
Interleukin-1 Inhibitor			
Anakinra	• Rheumatoid arthritis • Cryopyrin-associated periodic syndromes, specifically neonatal-onset multisystem inflammatory disease[23]	Competitively inhibits IL-1 binding to the IL-1 type I receptor	**For COVID-19** • A single-center case series reported on open-label use of anakinra in nine hospitalized patients with COVID-19, presenting with 4 days to 12 days of symptoms, requiring oxygen ≤6 L/minute, and serum CRP ≥50 mg/L. Anakinra was administered SQ, 100 mg every 12 hours for 3 days followed by 100 mg daily for up to 7 more days. Two of the nine patients also received HCQ plus AZM; the other 7 patients received no specific treatments. Anakinra was discontinued in one patient who progressed to acute respiratory failure after the first dose of the drug. Good clinical outcomes were observed in the other eight patients as assessed by oxygen flow, decline in CRP, and no progression in infiltrates on serial CT scans. Three patients experienced elevated liver transaminase levels. Results are difficult to interpret because of the low number of patients in the case series, the short follow-up, and the absence of a comparison group.[24]

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on *ClinicalTrials.gov*)
Interleukin-1 Inhibitor, continued			
Anakinra, continued			• A single-center retrospective cohort study in Italy compared outcomes in 29 patients following open-label anakinra use to outcomes in 16 historical controls. All patients had COVID-19 with moderate to severe ARDS requiring non-invasive ventilation, and evidence of hyperinflammation. High-dose IV anakinra 5 mg/kg twice daily (IV formulation is not approved in the United States) was administered for a median of 9 days, followed by SQ administration (anakinra 100 mg twice daily) for 3 days to avoid inflammatory relapses. Both the anakinra and control (standard treatment) groups received HCQ and LPV/r. In the high-dose anakinra group, reductions in CRP levels were noted following anakinra initiation. The 21-day survival was 90% in the anakinra group and 56% in the control group (P = 0.009); however, the patients in the anakinra group were younger (median 62 years vs. 70 years), and fewer had chronic kidney disease. High-dose anakinra was discontinued in seven patients (24%) due to AEs (bacteremia in four patients, elevated liver enzymes in three patients); 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.[25]
Interleukin-6 Inhibitors Elevations in IL-6 levels may be an important mediator when severe systemic inflammatory responses occur in some patients with COVID-19; IL-6 inhibition may reduce these effects.			
Sarilumab	Rheumatoid arthritis[26]	• Human recombinant monoclonal antibody • IL-6 receptor antagonist	**For COVID-19** • *Press Release:* In a Phase 2/3 clinical trial (*ClinicalTrials.gov* Identifier NCT04315298), hospitalized COVID-19 patients were randomized (2:2:1) to receive sarilumab 400 mg, sarilumab 200 mg, or placebo. Preliminary data were released after an IDMC recommended discontinuing the 200-mg arm and restricting future enrollment to critical patients only. Of the first 457 participants enrolled, 145 were randomized to sarilumab 400 mg, 136 to sarilumab 200 mg, and 77 to placebo. At study entry, 28% of the patients had severe illness, 49% had critical illness, and 23% had multisystem organ dysfunction. Sarilumab decreased CRP, which changed by -79%, -77%, and -21% in the sarilumab 400 mg group, sarilumab 200 mg group, and placebo group, respectively (primary outcome of the Phase 2 trial). At the time of data analysis, of the 226 critical patients, the proportion of patients who had died or were on a ventilator was lower in the sarilumab 400 mg group (28%) than in the sarilumab 200 mg group (46%) and in the placebo group (55%).

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on *ClinicalTrials.gov*)
Interleukin-6 Inhibitors, continued			
Sarilumab, continued			Comparing mortality alone, the proportion of patients who died was also lower in the sarilumab 400 mg group (23%) than in the sarilumab 200 mg group (36%) and in the placebo group (27%). In contrast to the positive trend in outcomes among the critical patients, the press release cited "negative trends" for most outcomes in severe patients who received sarilumab.[28]
Siltuximab	Multicentric Castleman disease	• Human-mouse chimeric monoclonal antibody • IL-6 antagonist[29]	**For COVID-19** • *Not Peer Reviewed:* In a single-center observational study of 21 patients with COVID-19 who developed pneumonia/ARDS and received treatment with IV siltuximab, some patients experienced decreased CRP levels (16 of 21 patients) and improved clinical condition (seven of 21 patients) following siltuximab treatment. Other patients experienced no clinically relevant change in condition (nine of 21 patients) or worsening condition (five of 21 patients). Among the five patients with worsening condition, there was one death and one cerebrovascular event (median follow-up of 8 days).[30]
Tocilizumab	• Cytokine release syndrome (induced by CAR T-cell therapy) • Rheumatoid arthritis • Giant cell arteritis • Polyarticular juvenile idiopathic arthritis • Systemic juvenile idiopathic arthritis[31]	• Recombinant humanized monoclonal antibody • IL-6 receptor antagonist	**For COVID-19** • *Press Release:* Early results were reported for the CORIMUNO-TOCI trial (*ClinicalTrials.gov* Identifier NCT04331808), an open-label randomized trial of hospitalized patients with COVID-19 (n = 129) at seven sites in France. The patients, who had moderate or severe disease at study entry, were randomized to receive tocilizumab plus SOC (n = 65) or SOC alone (n = 64). The dosing strategy was tocilizumab 8 mg/kg on Day 1; if there was no response (i.e., no decrease of oxygen requirement), a second infusion was repeated on Day 3. In this preliminary report, the proportion of participants who died or needed ventilation (noninvasive or mechanical) was lower in the tocilizumab group than in the SOC alone group. Detailed results of the trial have not been reported. • 63 hospitalized adult patients were enrolled in a prospective open-label study of tocilizumab for severe COVID-19. All patients received off-label ARV PIs. Patients received either tocilizumab IV (8 mg/kg) or SQ (324 mg); within 24 hours, a second dose was administered to 52 of the 63 patients. Following tocilizumab, fevers resolved in all but one patient, and CRP, ferritin, and D-dimer levels declined. The PaO_2/FiO_2 ratio increased between admission (152 +/-53 mm Hg) and Day 7 (284 +/-116 mm Hg). No moderate or severe AEs attributable to tocilizumab were reported. Overall mortality was 11% (seven deaths among the 63 patients). No details were provided regarding the rate of secondary infections after tocilizumab use. The authors report an association of reduced mortality with earlier use of

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
Interleukin-6 Inhibitors, continued			
Tocilizumab, continued			tocilizumab, but provide no details regarding a comparison group or specify an a-priori comparison, which limits interpretation of this result.[32] • An uncontrolled, retrospective cohort study of 21 hospitalized COVID-19 patients who received tocilizumab reported improvement in oxygenation and systemic inflammation.[33] At study entry, of the 21 patients (mean age 56 years; range 25 to 88 years), 17 had severe disease and four had critical disease. All patients were febrile, had abnormal chest CT findings, and required oxygen supplementation (two required mechanical ventilation). Mean CRP level was 75 mg/L, mean IL-6 expression level was 153 pg/mL, mean D-dimer level was 0.80 μg/mL, and mean lymphocyte percentage was 15.5%. Eighteen patients were given tocilizumab IV infusion once, and within 12 hours, three patients received a second infusion for indication of fever. Following tocilizumab administration, fevers normalized, lymphocyte percentages improved, and CRP levels declined. By Day 5, oxygen requirements were reduced in 15 of 20 participants (75%). There were no serious AEs attributed to tocilizumab, and no concurrent bacterial, fungal, or viral infections were observed during the treatment. The interpretability of this retrospective case series is limited due to its small sample size and lack of control group.
Janus Kinase Inhibitor			
Baricitinib	Rheumatoid arthritis[34]	• JAK inhibitor • Inhibition of kinases that regulate endocytosis (AAK1 and GAK) • Baricitinib is predicted to interfere with SARS-CoV-2 receptor-mediated endocytosis in lung AT2 alveolar epithelial cells.[35]	• No clinical data for COVID-19, SARS, or MERS • Baricitinib plasma concentrations are predicted to potentially be sufficient for AAK1 inhibition when administered at labeled dose (for the FDA-approved indication).[35]

Key: AAK1 = AP2-associated protein kinase 1; AE = adverse event; ARDS = acute respiratory distress syndrome; ARV = antiretroviral; AT2 = alveolar type 2; AZM = azithromycin; CAR = chimeric antigen receptor; CRP = C-reactive protein; CT = computerized tomography; FDA = Food and Drug Administration; GAK = cyclin G-associated kinase; HCQ = hydroxychloroquine; IDMC = independent data monitoring committee; IFN = interferon; IL = interleukin; IV = intravenous; IVIG = intravenous immune globulin; LPV/r = lopinavir/ritonavir; JAK = Janus kinase inhibitor; MERS = Middle East respiratory syndrome; MERS-CoV = Middle East respiratory syndrome coronavirus; PI = protease inhibitor; SARS = severe acute respiratory syndrome; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SQ = subcutaneous

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Table 3b. Characteristics of Immune-Based Therapy Under Evaluation for Treatment of COVID-19

(Last updated June 11, 2020)

- The information in this table is derived from data on the use of these drugs and biologic products for FDA-approved indications or in investigational trials; it is supplemented with data on their use in patients with COVID-19 where available.
- The effective dosing of these agents for treatment of COVID-19 is unknown. Therefore, the doses listed below are primarily derived from FDA-approved indications or from clinical trials investigating therapies for 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.
- Treatment-related AEs associated with immune-based therapy in patients with COVID-19 are not well defined. It is not known whether the frequency and severity of AEs in this population is similar to that in patient populations using these agents for FDA approved indications, especially in critically ill patients. Reported AEs of these drugs that are associated with long-term therapy (i.e., months to years) are not included in this table because treatment for COVID-19 is not long term. Please refer to product labels, when available.
- There are currently not enough data to determine whether certain medications can be safely coadministered with treatment for COVID-19. When using concomitant medications with similar toxicity profiles, consider additional safety monitoring.
- The potential additive, antagonistic, or synergistic effects and the safety of combination therapies for 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 labeling and visit the Liverpool COVID-19 Drug Interactions website.
- For information on drugs that prolong the QTc interval, please visit CredibleMeds.org.

Drug Name	Dosing Regimen *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.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Blood Products					
COVID-19 Convalescent Plasma and SARS-CoV-2 Immune Globulins	Single or multiple transfusions based on patient response	• TRALI and TACO have been reported.[1] • Fever, allergic reactions ranging from urticaria to anaphylaxis (rare) • Transmission of infectious pathogens • Antibody-mediated enhancement of infection • Red cell alloimmunization	Monitor for transfusion-related reactions. Observe the patient and measure vital signs at baseline and during and after transfusion.	Drug products **should not be added** to the IV infusion line for the blood product.	• There are insufficient data to recommend either for or against the use of COVID-19 convalescent plasma or SARS-CoV-2 immune globulins for the treatment of COVID-19. • The FDA has provided guidance for the use of COVID-19 convalescent plasma under an emergency IND application. • The FDA has approved a national expanded access program for the use of convalescent plasma for the treatment of patients with COVID-19. Clinicians can refer to the National COVID-19 Convalescent Plasma Project website for more information. People who have fully recovered from COVID-19 for at least 2 weeks and are interested in donating plasma can contact their local blood donor or plasma collection center or refer to the American Red Cross website. • A list of clinical trials is available: Convalescent Plasma and Immune Globulin

Drug Name	Dosing Regimen *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.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Blood Products, continued					
Non-SARS-CoV-2 Specific Intravenous Immune Globulin	Doses vary based on indication and formulation.	• Thrombotic events • Renal dysfunction and acute renal failure (more common with certain products) • Flu-like symptoms, dermatologic effects, arrhythmia, TRALI, anaphylaxis, aseptic meningitis, and hemolysis • AEs may be precipitated by high dose, rapid infusion, or underlying conditions, including IgA-deficiency. AEs may vary between formulations. • Consider the risks and benefits of the high-dose regimen in patients with increased risk of thrombosis, hemolysis, acute kidney injury, or volume overload.	• Observe the patient and measure vital signs at baseline and during and after infusion. • Discontinue if renal function deteriorates during treatment.	IVIG may interfere with immune response to certain vaccines.	• The Panel **recommends against** the use of non-SARS-CoV-2 specific IVIG for the treatment of COVID-19, except in a clinical trial **(AIII)**. This should not preclude the use of IVIG when otherwise indicated for treatment of complications that arise during COVID-19. • A list of clinical trials is available: Intravenous Immunoglobulin

Drug Name	Dosing Regimen *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.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Interferons					
Interferon Alfa	Peginterferon alfa-2a 180 mcg SQ once weekly for 2 weeks for MERS[2,3]	Flu-like symptoms (e.g., fever, fatigue, myalgia), injection site reactions, liver function abnormalities, decreased blood counts, worsening of depression, insomnia, irritability, nausea, vomiting, and hypertension[4]	• CBC with differential • LFTs (ALT); avoid if Child-Pugh Score >6 • Depression, psychiatric symptoms • Reduce dose in patients with CrCl <30 mL/min.	• Low potential for drug interactions • Inhibition of CYP1A2	• The Panel **recommends against** the use of IFN alfa, except in a clinical trial **(AIII)**. • For MERS, SQ formulation used in combination with ribavirin. • Use with caution with other hepatotoxic agents. • Reduce dose if ALT >5 times ULN; discontinue if accompanied by increase in bilirubin. • Reduce dose or discontinue if neutropenia or thrombocytopenia occur. • A list of clinical trials is available: Interferon
Interferon Beta	**IFN Beta-1a:** • 44 mcg SQ three times weekly[3] for MERS • Duration for COVID-19 unknown • SNG001 (this formulation delivered by nebulization is not approved in the United States). **IFN Beta-1b:** • 0.25 mg SQ every 48 hours for MERS[5] • Duration unknown	Flu-like symptoms (e.g., fever, fatigue, myalgia), leukopenia, neutropenia, thrombocytopenia, lymphopenia, increased liver enzymes (ALT > AST), injection site reactions, headache, hypertonia, pain, rash, and worsening of depression[6,7]	• LFTs • CBC with differential • Worsening CHF • Depression, suicidal ideation	Low potential for drug interactions	• The Panel **recommends against** use of IFN beta, except in a clinical trial **(AIII)**. • Use with caution with other hepatotoxic agents. • Reduce dose if ALT >5 times ULN. • Several products are available in the United States; doses differ between products. **IFN Beta-1a Products:** • Avonex, Rebif **IFN Beta-1b Products:** • Betaseron, Extavia • A list of clinical trials is available: Interferon

Drug Name	Dosing Regimen *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.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Interleukin-1 Inhibitor					
Anakinra	• Standard adult dose is 100 mg SQ once daily • Duration unknown	• Neutropenia (particularly in combination with other agents that can cause neutropenia) • Anaphylaxis • Headache, nausea, diarrhea, sinusitis, arthralgia, flu-like symptoms, and abdominal pain • Injection site reactions	• CBC • Renal function (reduce dose in patients with CrCl <30 mL/min)	Use with TNF-blocking agents **is not recommended** due to increased risk of infection.	• There are insufficient data for the Panel to recommend for or against the use of IL-1 inhibitors (e.g., anakinra) for the treatment of COVID-19. • A list of clinical trials is available: Anakinra
Interleukin-6 Inhibitors					
Sarilumab[8]	**Clinical Trial Dosing (See NCT04315298):** • 400 mg IV vs. placebo (single dose)[9] **Note:** The only FDA-approved sarilumab product is an SQ formulation.	• Neutropenia, thrombocytopenia • Gastrointestinal perforation • HSR • Increased ALT and AST • Hepatitis B reactivation • Infusion reaction possible	• Monitor for HSR • Monitor for infusion reaction • Neutrophils, platelets, liver function	• 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.	• There are insufficient data for the Panel to recommend for or against the use of sarilumab for the treatment of COVID-19. • A list of clinical trials is available: Sarilumab
Siltuximab	• 11 mg/kg IV over 1 hour every 3 weeks for multicentric Castleman disease[10] • Dose and duration for COVID-19 unknown	• Infusion-related reaction • Gastrointestinal perforation • Neutropenia • Hypertension	• Hypersensitivity • Monitor for infusion reaction • Neutrophils	• Elevated IL-6 may downregulate CYP enzymes; use of siltuximab may lead to increased metabolism of drugs that are CYP450 substrates.	• There are insufficient data for the Panel to recommend for or against the use of siltuximab for the treatment of COVID-19. • May mask signs of acute inflammation (i.e., suppression of fever and CRP) • A list of clinical trials is available: Siltuximab

Drug Name	Dosing Regimen *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.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Interleukin-6 Inhibitors, continued					
Siltuximab, continued		• Dizziness • Rash • Pruritus • Hyperuricemia		• Effects on CYP450 may persist for weeks after therapy.	
Tocilizumab[11]	**Clinical Trial Dosing:** • 8 mg/kg IV once • Dose **should not exceed** 800 mg. • Dose may be repeated once, 12 hours later, if clinical symptoms worsen or show no improvement (see NCT04320615).	• Infusion-related reactions • HSR • Gastrointestinal perforation • Hepatotoxicity • Treatment-related changes in neutrophils, platelets, lipids, and LFTs • Hepatitis B reactivation	• Monitor for HSR • Monitor for infusion reactions • Neutrophils, platelets • LFTs	• 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.	• There are insufficient data for the Panel to recommend for or against the use of tocilizumab for the treatment of COVID-19. • SQ formulation **is not intended** for IV administration. • A list of clinical trials is available: Tocilizumab
Janus Kinase Inhibitor					
Baricitinib[12]	• 2 mg PO once daily for rheumatoid arthritis • Duration unknown	• Lymphoma and other malignancies • Thrombosis • Gastrointestinal perforation • Treatment-related changes in lymphocytes, neutrophils, hemoglobin, liver enzymes • Herpes simplex • Herpes zoster	• Treatment-related decreases in neutrophils, lymphocytes, and hemoglobin • Renal and hepatic function • Monitor for new infections	Dose modification is recommended when concurrently administering with a strong OAT3 inhibitor.	• The Panel **recommends against** the use of baricitinib, except in a clinical trial **(AIII)**. • **Not recommended** in patients with severe hepatic or renal impairment. • A list of clinical trials is available here: Baricitinib

Key: AE = adverse effect; ALT = alanine transaminase; AST = aspartate aminotransferase; CBC = complete blood count; CHF = congestive heart failure; CrCl = creatinine clearance; CRP = C-reactive protein; CYP = cytochrome P; FDA = Food and Drug Administration; HSR = hypersensitivity reaction; IFN = interferon; IgA = immunoglobulin A; IL-1 = interleukin-1; IL-6 = interleukin-6; IND = Investigational New Drug; IV = intravenous; IVIG = intravenous immunoglobulin; LFT = liver function test; MERS = Middle East respiratory syndrome; OAT = organic anion transporter; PO = orally; SARS = severe acute respiratory syndrome; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SQ = subcutaneous; TACO = transfusion-related circulatory overload; the Panel = the COVID-19 Treatment Guidelines Panel; 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 May 12, 2020)

Summary Recommendations

Laboratory Testing:

- In non-hospitalized 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 for or against using this data to guide management decisions **(BIII)**.

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 non-hospitalized patients with COVID-19, anticoagulants and antiplatelet therapy should not be initiated for prevention of venous thromboembolism (VTE) or arterial thrombosis unless there are other indications **(AIII)**.
- Hospitalized adults with COVID-19 should receive VTE prophylaxis per the standard of care for other hospitalized adults **(AIII)**. A diagnosis of COVID-19 should not influence a pediatrician's recommendations about VTE prophylaxis in hospitalized children **(BIII)**. 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)**.
- Reported incidence of VTE in hospitalized patients with COVID-19 varies. There are currently insufficient data to recommend for or against the use of thrombolytics or increasing anticoagulant doses for VTE prophylaxis in hospitalized COVID-19 patients outside the setting of a clinical trial **(BIII)**.
- Hospitalized patients with COVID-19 should not routinely be discharged on VTE prophylaxis **(AIII)**. Using Food and Drug Administration-approved regimens, extended VTE prophylaxis can be considered in patients who are at low risk for bleeding and high risk for VTE as per protocols for patients without COVID-19 (see text for details on defining at-risk patients) **(BI)**.
- There are currently insufficient data to recommend 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 **(BIII)**.
- For hospitalized COVID-19 patients, the possibility of thromboembolic disease should be evaluated in the event of rapid deterioration of pulmonary, cardiac, or neurological function, or of sudden, localized loss of peripheral perfusion **(AIII)**.

Treatment:

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

Special Considerations During Pregnancy and Lactation:

- Management of anticoagulation therapy during labor and delivery requires specialized care and planning and should be managed similarly in pregnant patients with COVID-19 as 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 in breastfeeding women with or without COVID-19 who require VTE prophylaxis or treatment **(AIII)**. In contrast, direct-acting oral anticoagulants are 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 with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion

Association Between COVID-19 and Thromboembolism

Infection with the novel coronavirus SARS-CoV-2 and the resulting syndrome coronavirus disease (COVID-19) has been associated with inflammation and a prothrombotic state, with increases in fibrin, fibrin degradation products, fibrinogen, and D-dimers.[1,2] In fact, these markers have been associated with worse clinical outcomes.[3,4] Although the true incidence of these complications among those with different severities of disease is not completely defined, there have been reports of increased incidence of thromboembolic disease associated with COVID-19 in patients in the intensive care unit (ICU).[5,6] In a French prospective multicenter cohort of 150 ICU patients, 16.7% had pulmonary embolism despite prophylactic anticoagulation. Patients with COVID-19 and acute respiratory distress syndrome (ARDS) had increased incidence of pulmonary embolism compared to patients without COVID-19-associated ARDS.[6] A Dutch study of 184 ICU patients reported a cumulative incidence of venous thromboembolism (VTE) of 27% (95% confidence interval, 17% to 32%), despite prophylaxis.[7] A study that used routine ultrasounds reported VTE incidence of 69%[5] in those admitted to the ICU. However, other centers have reported lower event rates. An Italian study found a VTE rate of 22.2%.[8] Among 393 patients from New York, only 13 patients (3.3%) experienced VTE; 10 of those patients (7.7%) were mechanically ventilated, and three (1.1%) were not mechanically ventilated.[9] Epidemiologic studies that control for clinical characteristics, underlying comorbidities, prophylactic anticoagulation, and COVID-19-related therapies are needed.

Notably, all of the studies described above relied on clinical findings that were suggestive of thromboembolic events to trigger a diagnosis of thromboembolism. Although the incidence of thromboembolic events, especially pulmonary emboli, can be quite high, there are, as of yet, no published data investigating the utility of routine surveillance for deep vein thrombosis via lower extremity ultrasound. However, for clinicians who routinely perform ultrasound examinations in critically ill patients, adding deep veins to the daily examination could be a useful adjunct to care.

There remains very little prospective data demonstrating the benefits of monitoring coagulation markers or the safety and efficacy of using therapeutic doses of anticoagulants in those with COVID-19 in the absence of other indications. A retrospective analysis of 2,773 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% who received anticoagulation and 62.7% 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.[10]

A number of 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). Interim guidance on recognizing and managing coagulopathy in patients with COVID-19 has been released by the International Society of Thrombosis and Haemostasis (ISTH).[11] The American Society of Hematology has developed guidance statements about coagulopathy and venous thromboembolism. An additional 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.[12]

Monitoring Coagulation Markers in Patients with COVID-19:

- Non-hospitalized patients with COVID-19 should not routinely be tested for measures of coagulopathy, such as D-dimer level, prothrombin time, fibrinogen level, and platelet count **(AIII)**. Although abnormalities of these markers have been associated with worse outcomes, there is a lack of prospective data demonstrating that they can be used for risk stratification in those who are asymptomatic or those with mild SARS-CoV-2 infection.
- Hematologic and coagulation parameters are commonly measured in hospitalized patients with COVID-19. Nevertheless, there are currently insufficient data to recommend for or against using such data to guide management decisions **(BIII)**.

Managing Coagulopathy in Patients with COVID-19

Selection of Anticoagulant or Antiplatelet Drugs for Patients with COVID-19:[13]

- Any time anticoagulant or antiplatelet therapy is being used, consideration must be given to potential drug-drug interactions with other concomitant drugs **(AIII)**. The University of Liverpool has collated a list of drug interactions.
- Low molecular weight heparin or unfractionated heparin may be preferred in hospitalized, critically ill patients because of their shorter half-lives, ability to be administered intravenously or subcutaneously, and fewer drug-drug interactions compared with oral anticoagulants **(AIII)**.
- Outpatients receiving warfarin who are unable to get international normalized ratio monitoring during isolation may be candidates for direct oral anticoagulant therapy. Patients with mechanical heart valves, ventricular assist devices, valvular atrial fibrillation, or antiphospholipid antibody syndrome or patients who are lactating should continue treatment with warfarin therapy **(AIII)**.

Chronic Anticoagulant or Antiplatelet Therapy:

- Patients with COVID-19 who are taking anticoagulant or antiplatelet therapy for underlying medical conditions should continue their treatment unless significant bleeding develops or other contraindications are present **(AIII)**.

Patients with COVID-19 Who Are Managed as Outpatients:

- For non-hospitalized patients with COVID-19, anticoagulant or antiplatelet therapy should not be initiated for VTE prophylaxis or at therapeutic doses **(AIII)**.

Hospitalized Patients with COVID-19:

- For adults who are admitted to a hospital with COVID-19, VTE prophylaxis, unless contraindicated (e.g., a patient has active hemorrhage or severe thrombocytopenia), should be prescribed using the recommendations for patients who have been admitted to a hospital for other indications **(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]
- A recent meta-analysis of COVID-19 infection in children did not discuss venous thromboembolism.[14] Given insufficient data, COVID-19 infection should not change VTE prophylaxis recommendations for hospitalized children **(BIII)**.
- Anticoagulant or antiplatelet therapy should not be used to prevent arterial thrombosis outside of the standard of care for those without COVID-19 **(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.

- Patients with COVID-19 who experience an incident thromboembolic event or who are highly suspected to have thromboembolic disease at a time when imaging is not possible 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 using therapeutic doses of antithrombotic or thrombolytic agents for COVID-19 in patients who are admitted to a hospital **(BIII)**. While there is evidence that multi-organ failure is more likely in patients with sepsis if they develop coagulopathy,[15] there are 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, if trials are available.
- 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 as per the standard institutional protocols for those without COVID-19 **(AIII)**.

Patients with COVID-19 Who Are Discharged from the Hospital:

- Routine post-discharge VTE prophylaxis **is not recommended** for patients with COVID-19 **(AIII)**. However, the benefits of post-discharge prophylaxis for certain high-risk patients without COVID-19 led to the Food and Drug Administration approval of two regimens: rivaroxaban 10 mg daily for 31 to 39 days, and betrixaban 160 mg on Day 1, followed by betrixaban 80 mg once daily for 35 to 42 days.[16,17] Inclusion criteria for the trials that studied these regimens included:
  - Modified IMPROVE-VTE score ≥4; *or*
  - Modified IMPROVE-VTE score ≥2 and D-dimer level >2 times the upper limit of normal;[16] *or*
  - Age ≥75 years; *or*
  - Age >60 years and D-dimer level >2 times the upper limit of normal; *or*
  - Age 40 to 60 years, D-dimer level >2 times the upper limit of normal, and previous VTE event or cancer.[17]
- Any decision to use post-discharge VTE prophylaxis should consider the individual patient's risk factors, including reduced mobility, bleeding risks, and feasibility.

Special Considerations for Pregnancy and Lactation

Several professional societies, including the American Society of Hematology and the American College of Obstetricians and Gynecologists, have guidelines that specifically address management of VTE in the context of pregnancy.[18,19] There is a lack of data on the use of these scoring systems to predict VTE risk in pregnant people. Additionally, the D-dimer level may not be a reliable predictor of VTE in pregnancy, because there is a physiologic increase of D-dimer levels throughout gestation.[20-22]

In general, the preferred anticoagulants during pregnancy are heparin compounds.[2] Because of its reliability and ease of administration, low-molecular weight heparin is recommended rather than unfractionated heparin for prevention and treatment of VTE in pregnancy.[19]

Direct-acting anticoagulants are not routinely used during pregnancy due to the lack of safety data in pregnant people.[18] The use of warfarin for the prevention or treatment of VTE should be avoided in pregnant people, regardless of their COVID-19 status; this is especially true during the first trimester, due to the concern for teratogenicity.

Specific recommendations for pregnant women with COVID-19 include:

- If antithrombotic therapy is prescribed during pregnancy for another indication, this therapy should be continued if the patient receives a diagnosis of COVID-19 **(AIII)**.
- For pregnant patients admitted to the hospital with COVID-19, recommendations for VTE prophylaxis are the same as those for hospitalized nonpregnant patients **(AIII)**.
- Management of anticoagulation therapy during labor and delivery requires specialized care and planning and should be managed similarly in pregnant patients with COVID-19 as other conditions that require anticoagulation in pregnancy **(AIII)**.

Thrombolytic Therapy in Pregnancy:

Due to the potential risk of maternal hemorrhage, during pregnancy, thrombolytic therapy should be reserved for acute pulmonary embolism with life-threatening hemodynamic instability regardless of whether a patient has COVID-19 **(AIII)**.[18]

Lactation:

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 in breastfeeding women with or without COVID-19 who require VTE prophylaxis or treatment **(AIII)**.[19] In contrast, direct-acting oral anticoagulants are not routinely recommended due to the lack of safety data **(AIII)**.[18]

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Considerations for Certain Concomitant Medications in Patients with COVID-19

(Last updated June 25, 2020)

Summary Recommendations

Angiotensin-Converting Enzyme (ACE) Inhibitors and Angiotensin Receptor Blockers (ARBs):

- Persons with COVID-19 who are prescribed ACE inhibitors or ARBs for cardiovascular disease (or other indications) should continue these medications **(AIII)**.
- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of ACE inhibitors or ARBs for the treatment of COVID-19 outside of the setting of a clinical trial **(AIII)**.

Corticosteroids

For Management of COVID-19:

- The Panel recommends using dexamethasone (at a dose of 6 mg per day for up to 10 days) in patients with COVID-19 who are mechanically ventilated **(AI)** and in patients with COVID-19 who require supplemental oxygen but who are not mechanically ventilated **(BI)**.
- The Panel **recommends against** using dexamethasone in patients with COVID-19 who do not require supplemental oxygen **(AI)**.
- See the Panel's guidance on the use of dexamethasone for a detailed discussion of these recommendations.

For Patients on Chronic Corticosteroids:

- Oral corticosteroid therapy that was used prior to COVID-19 diagnosis for another underlying condition (e.g., primary or secondary adrenal insufficiency, rheumatological diseases) should not be discontinued **(AIII)**. On a case-by-case basis, supplemental or stress-dose steroids may be indicated **(AIII)**.
- Inhaled corticosteroids that are used daily for patients with asthma and chronic obstructive pulmonary disease for control of airway inflammation should not be discontinued in patients with COVID-19 **(AIII)**.

Pregnancy Considerations:

- The antenatal corticosteroids betamethasone and dexamethasone are known to cross the placenta and are therefore generally reserved for when administration is required for fetal benefit **(BIII)**. Other systemic corticosteroids do not cross the placenta, and pregnancy is not a reason to restrict their use if otherwise indicated **(CIII)**.
- The American College of Obstetricians and Gynecologists **recommends against** offering antenatal corticosteroids for fetal benefit in the late preterm period (34 0/7 weeks–36 6/7 weeks) because the benefits of antenatal corticosteroids in the late preterm period are less well established **(CIII)**.
- Modifications to care for these patients and the use of corticosteroids that cross the placenta may be individualized, weighing the neonatal and maternal benefits of antenatal corticosteroid use with the risks of potential harm to the pregnant patient **(CIII)**.

HMG-CoA Reductase Inhibitors (Statins):

- Persons with COVID-19 who are prescribed statin therapy for the treatment or prevention of cardiovascular disease should continue these medications **(AIII)**.
- The Panel **recommends against** the use of statins for the treatment of COVID-19 outside the setting of a clinical trial **(AIII)**.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs):

- Persons with COVID-19 who are taking NSAIDs for a comorbid condition should continue therapy as previously directed by their physician **(AIII)**.
- The Panel recommends that there be no difference in the use of antipyretic strategies (e.g., with acetaminophen or NSAIDs) between patients with or without COVID-19 **(AIII)**.

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

Recommendations:

- Persons with COVID-19 who are prescribed angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) for cardiovascular disease (or other indications) should continue these medications **(AIII)**.
- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of ACE inhibitors or ARBs for the treatment of COVID-19 outside the setting of a clinical trial **(AIII)**.

Angiotensin-converting enzyme 2 (ACE2) is the cell surface receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It has been hypothesized[1] that the modulation of ACE2 associated with these therapies could suppress or enhance SARS-CoV-2 replication.[2] Investigations of the role of ARBs and recombinant human ACE2 in treatment and prevention of SARS-CoV-2 infection are underway.[3]

Whether these medications are helpful, harmful, or neutral in the pathogenesis of SARS-CoV-2 infection is unclear. Currently, there is a lack of sufficient clinical evidence demonstrating that ACE inhibitors or ARBs have any impact on the susceptibility of individuals to SARS-CoV-2 or on the severity or outcomes of infection. This recommendation is in accord with a joint statement of the American Heart Association, the Heart Failure Society of America, and the American College of Cardiology.[3]

Corticosteroids

It has been proposed that the anti-inflammatory effects of corticosteroids have a potential therapeutic role in suppressing cytokine-related lung injury in patients with COVID-19.[4] Data from other respiratory infections have shown that systemic corticosteroids can affect the pathogenesis of these infections in various ways. In outbreaks of other novel coronavirus infections[5,6] (i.e., Middle East respiratory syndrome [MERS] and severe acute respiratory syndrome [SARS]), corticosteroid therapy was associated with delayed virus clearance. In severe pneumonia caused by influenza, corticosteroid therapy may worsen clinical outcomes, including secondary bacterial infection and mortality.[7]

Preliminary clinical trial data from a large, randomized, open-label trial suggest that dexamethasone reduces mortality in hospitalized patients with COVID-19 who require mechanical ventilation or supplemental oxygen.[8] The recommendations for using corticosteroids in patients with COVID-19 depend on the severity of illness. Before initiating dexamethasone, clinicians should review the patient's medical history and assess the potential risks and benefits of administering corticosteroids to the patient.

For Management of COVID-19

- The Panel recommends using dexamethasone (at a dose of 6 mg per day for up to 10 days) in patients with COVID-19 who are mechanically ventilated **(AI)** and in patients with COVID-19 who require supplemental oxygen but who are not mechanically ventilated **(BI)**.
- The Panel **recommends against** using dexamethasone in patients with COVID-19 who do not require supplemental oxygen **(AI)**.

See the Panel's guidance on the use of dexamethasone for a detailed discussion of these recommendations.

Patients on Chronic Systemic Corticosteroid Therapy

Patients with COVID-19 may also be receiving systemic corticosteroid therapy for a variety of underlying conditions.

Recommendation

- Oral corticosteroid therapy that was used prior to COVID-19 diagnosis for another underlying condition (e.g., primary or secondary adrenal insufficiency, rheumatological diseases) should not be discontinued **(AIII)**.[9] On a case-by-case basis, supplemental or stress-dose steroids may be indicated **(AIII)**.

Patients on Inhaled Corticosteroids

Recommendation

- Inhaled corticosteroids that are used daily for patients with asthma and chronic obstructive pulmonary disease for control of airway inflammation should not be discontinued in patients with COVID-19 **(AIII)**. No studies to date have investigated the relationship between inhaled corticosteroids in these settings and virus acquisition, severity of illness, or viral transmission.

Pregnancy Considerations

The antenatal corticosteroids betamethasone and dexamethasone are known to cross the placenta and are therefore generally reserved for when administration is required for fetal benefits **(BIII)**. Other systemic corticosteroids do not cross the placenta, and pregnancy is not a reason to restrict their use if otherwise indicated.[10]

HMG-CoA Reductase Inhibitors (Statins)

Recommendations

- Persons with COVID-19 who are prescribed statin therapy for the treatment or prevention of cardiovascular disease should continue these medications **(AIII)**.
- The Panel **recommends against** the use of statins for the treatment of COVID-19 outside the setting of 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.[11] Observational studies have reported that statin therapy may reduce cardiovascular morbidity in patients admitted with other respiratory infections, such as influenza and bacterial pneumonia.

Nonsteroidal Anti-Inflammatory Drugs

Recommendations

- Persons with COVID-19 who are taking nonsteroidal anti-inflammatory drugs (NSAIDs) for a co-morbid condition should continue therapy as previously directed by their physician **(AIII)**.
- The Panel recommends that there be no difference in the strategy of antipyretic use (e.g., with acetaminophen or NSAIDs) as in patients with or without COVID-19 **(AIII)**.

In mid-March 2020, news agencies promoted reports that anti-inflammatory drugs may worsen COVID-19. It has been proposed that NSAIDs like ibuprofen can increase the expression of ACE2[1] and inhibit antibody production.[12] 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.[13]

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Appendix A, Table 1. COVID-19 Treatment Guidelines Panel Members

(Last updated June 11, 2020)

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Phyllis Tien, MD, MSc	University of California, San Francisco/San Francisco VA Healthcare System, San Francisco, CA
Alpana A. Waghmare, MD	Seattle Children's Hospital, Seattle, WA
Kevin C. Wilson, MD	Boston University School of Medicine, Boston, MA
Ex-Officio Members, U.S. Government Representatives	
Timothy Burgess, MD	Department of Defense, Bethesda, MD
Joseph Francis, MD, MPH	Department of Veterans Affairs, Washington, DC
Virginia Sheikh, MD, MHS	Food and Drug Administration, Silver Spring, MD
Timothy M. Uyeki, MD, MPH	Centers for Disease Control and Prevention, Atlanta, GA
Robert Walker, MD	Biomedical Advanced Research and Development Authority, Washington, DC
U.S. Government Support Team	
Laura Bosque Ortiz, BS	National Institutes of Health, Bethesda, MD
John T. Brooks, MD	Centers for Disease Control and Prevention, Atlanta, GA
Richard T. Davey, Jr., MD	National Institutes of Health, Bethesda, MD
Laurie K. Doepel, BA	National Institutes of Health, Bethesda, MD
Robert W. Eisinger, PhD	National Institutes of Health, Bethesda, MD
Elizabeth S. Higgs, MD, DTM&H, MIA	National Institutes of Health, Bethesda, MD
Martha C. Nason, PhD	National Institutes of Health, Bethesda, MD
Kanal Singh, MD, MPH	National Institutes of Health, Bethesda, MD
Assistant Executive Secretaries	
Page Crew, PharmD, MPH	National Institutes of Health, Bethesda, MD
Safia Kuriakose, PharmD	Leidos Biomedical Research, Inc., in support of NIAID, Frederick, MD
Andrea M. Lerner, MD, MS	National Institutes of Health, Bethesda, MD

Appendix A, Table 2. COVID-19 Treatment Guidelines Panel Financial Disclosure for Companies Related to COVID-19 Treatment or Diagnostics (Reporting Period: May 1, 2019, to March 31, 2020)

(Last updated June 11, 2020)

Panel Member	Financial Disclosure	
	Company	Relationship
Judith Aberg, MD	Gilead Sciences	Research Support
	Regeneron	Research Support
Adaora Adimora, MD, MPH	Gilead Sciences	Consultant, Research Support
Jason Baker, MD, MS	Gilead Sciences	Research Support
Lisa Baumann Kreuziger, MD, MS	3M	Stockholder, spouse is an employee
	CSL Behring	Advisory Board for Non-Approved Medications
	Quercegen Pharmaceuticals	Advisory Board for Non-Approved Medications
	Versiti	Employee
Roger Bedimo, MD, MS	Gilead Sciences	Honoraria
Pamela S. Belperio, PharmD	None	N/A
Laura Bosque Ortiz, BS	None	N/A
John T. Brooks, MD	None	N/A
Timothy Burgess, MD	None	N/A
Stephen V. Cantrill, MD	None	N/A
Ann C. Collier, MD	None	N/A
Craig Coopersmith, MD	None	N/A
Page Crew, PharmD, MPH	None	N/A
Eric Daar, MD	Gilead Sciences	Consultant, Research Support
Richard T. Davey, Jr., MD	None	N/A
Susan L. Davis, PharmD	None	N/A
Laurie K. Doepel, BA	None	N/A
Amy L. Dzierba, PharmD	None	N/A
Robert W. Eisinger, PhD	None	N/A
Laura Evans, MD, MSc	None	N/A
Joseph Francis, MD, MPH	None	N/A
Rajesh Gandhi, MD	Merck & Co.	Advisory Board
David V. Glidden, PhD	Gilead Sciences	Consultant
Birgit Grund, PhD	None	N/A
Roy M. Gulick, MD, MPH	None	N/A
Erica J. Hardy, MD, MMSc	None	N/A
Elizabeth S. Higgs, MD, DTM&H, MIA	None	N/A
Brenna L. Hughes, MD, MSc	None	N/A
Steven Johnson, MD	None	N/A

Panel Member	Financial Disclosure	
	Company	Relationship
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	None	N/A
Gregory Martin, MD, MSc	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	None	N/A
Alice K. Pau, PharmD	None	N/A
Andrew T. Pavia, MD	Genentech	Consultant
	Merck & Co.	Consultant
	Seqirus	Consultant
Nitin Seam, MD	None	N/A
Virginia Sheikh, MD, MHS	None	N/A
Steven Q. Simpson, MD	None	N/A
Kanal Singh, MD, MPH	None	N/A
Susan Swindells, MBBS	None	N/A
Pablo Tebas, MD	Gilead Sciences	Research Support
	INOVIO Pharmaceuticals	Research Support
Phyllis Tien, MD, MSc	None	N/A
Timothy M. Uyeki, MD, MPH	None	N/A
Alpana A. Waghmare, MD	Ansun BioPharma	Research Support
	KYORIN Pharmaceutical Co.	Advisory Board
Robert Walker, MD	None	N/A
Kevin C. Wilson, MD	None	N/A