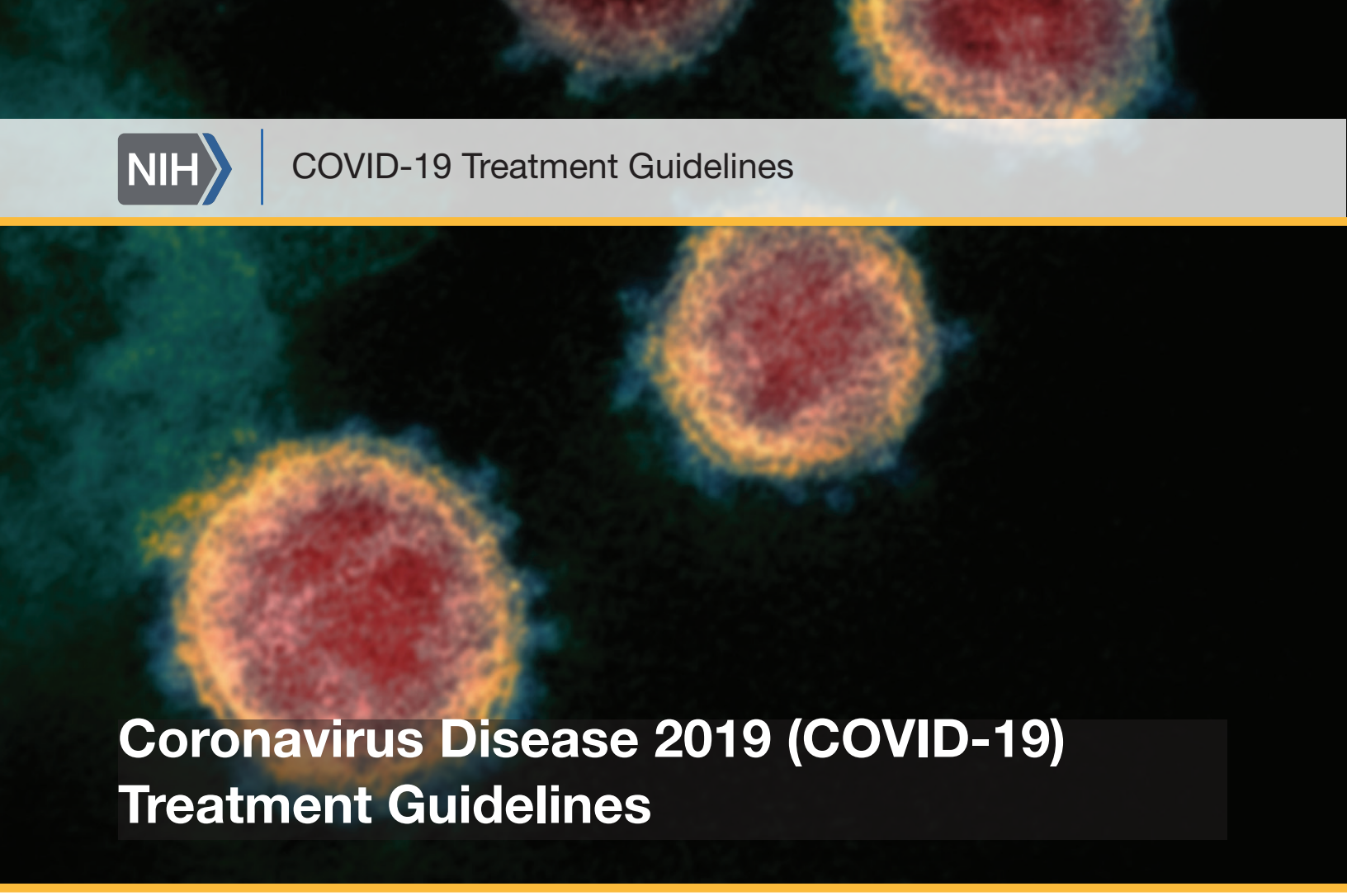

Coronavirus Disease 2019 (COVID-19) Treatment Guidelines

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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What's New in the Guidelines

Last Updated: July 17, 2020

Key Updates to the Guidelines

Remdesivir

In situations where remdesivir supplies are limited, the COVID-19 Treatment Guidelines Panel (the Panel) recommends prioritizing **remdesivir** for use in hospitalized patients with COVID-19 who require supplemental oxygen but who are not mechanically ventilated or on extracorporeal membrane oxygenation **(BI)**. The overall recommendations for the use of remdesivir are being revised and will be updated soon.

Corticosteroids (Including Dexamethasone)

The Corticosteroids (Including Dexamethasone) section is a new subsection of Immunomodulators Under Evaluation for Treatment of COVID-19. This new section is based on the Recommendations for Dexamethasone in Patients with COVID-19 section that was released on June 25, 2020. The Panel continues to recommend the use of **dexamethasone** in patients who are mechanically ventilated **(AI)** and in patients who require supplemental oxygen but who are not mechanically ventilated **(BI)**. The new Corticosteroids (Including Dexamethasone) section also discusses the clinical data on the use of other corticosteroids in patients with COVID-19, the potential adverse effects of corticosteroids, other considerations when using corticosteroids, and recommendations for the use of dexamethasone in pregnant patients.

New Sections of the Guidelines

Mesenchymal Stem Cells

A new subsection on mesenchymal stem cells was added to Immune-Based Therapy in the Blood-Derived Products Under Evaluation for the Treatment of COVID-19 section. The Panel **recommends against** the use of **mesenchymal stem cells** for the treatment of COVID-19, except in a clinical trial **(AII)**.

Adjunctive Therapy: Vitamin C, Vitamin D, and Zinc Supplementation

Vitamin and mineral supplements have been promoted for the treatment and prevention of respiratory viral infections; however, their roles in treating COVID-19 are yet unproven. Three new sections were added to the guidelines to discuss the proposed rationale for the use of vitamin C, vitamin D, and zinc supplements.

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

Solid organ transplant, hematopoietic stem cell transplant, and cellular therapy donors and recipients are at risk of complications associated with COVID-19. This new section provides recommendations for screening transplant candidates and donors for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection before donation and transplant. Clinicians should follow the guidelines for evaluating and managing COVID-19 in nontransplant patients when treating transplant and cellular therapy recipients **(AIII)**. In this section, the Panel also emphasizes the importance of consulting a transplant specialist and reviewing concomitant medications for drug-drug interactions and overlapping toxicities.

Other Updates to the Guidelines

Introduction

The Panel has expanded the explanation of the types of recommendation statements used in the guidelines.

Overview of COVID-19: Epidemiology, Clinical Presentation, and Transmission

The section has been updated with recent epidemiologic data on COVID-19 in the United States. Emerging evidence suggests that racial and ethnic minorities in the United States experience higher rates of COVID-19 and subsequent hospitalization and death.

Prevention and Prophylaxis of SARS-CoV-2 Infection

This section discusses general prevention measures for reducing the risk of acquisition and transmission of SARS-CoV-2, the types of vaccines that are currently being studied, and the drug therapies that are being investigated for pre-exposure and post-exposure prophylaxis.

Hydroxychloroquine Plus Azithromycin

New clinical data from a large, retrospective, observational study have been added to this section and Table 2A. There is no change to the Panel's recommendation.

Lopinavir/Ritonavir and Other HIV Protease Inhibitors

New data on lopinavir/ritonavir pharmacokinetics in patients with COVID-19 and new data on combination therapy with lopinavir/ritonavir plus interferon beta-1b plus ribavirin for the treatment of COVID-19 have been added to this section and Table 2A. There is no change to the Panel's recommendation.

Blood-Derived Products Under Evaluation for the Treatment of COVID-19

New clinical data have been added to the Convalescent Plasma section. A new section has been created for SARS-CoV-2-specific immunoglobulins. There are no changes to the Panel's recommendations.

Immunomodulators Under Evaluation for the Treatment of COVID-19

New clinical data for interferon beta-1b were added to the Interferons (Alfa, Beta) section, and the Panel changed the recommendation for interferons: The Panel **recommends against** the use of interferons for the treatment of severe and critically ill COVID-19 patients, except in a clinical trial **(AIII)**. There are insufficient data to recommend either for or against the use of **interferon-beta** for the treatment of early (<7 days from symptom onset) mild and moderate COVID-19.

The Kinase Inhibitors section was expanded to include additional Janus kinase (JAK) inhibitors and to include Bruton's tyrosine kinase (BTK) inhibitors. The Panel **recommends against** the use of **BTK inhibitors** and **JAK inhibitors** for the treatment of COVID-19, except in a clinical trial **(AIII)**.

Introduction

Last Updated: July 17, 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 become 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 cochairs 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 financial disclosures of the members and *ex officio* members of the Panel and members of the support team are provided in the Panel Roster and Financial Disclosure sections of the Guidelines.

Development of the Guidelines

Each section of the Guidelines is developed by a working group of Panel members with expertise in the area addressed in the section. Each working group is responsible for identifying relevant information and

published scientific literature and for conducting a systematic, comprehensive review of that information and literature. The working groups propose updates to the Guidelines based on the latest published research findings and evolving clinical information.

New Guidelines sections and recommendations are reviewed and voted on by the voting members of the Panel. To be included in the Guidelines, a recommendation must be endorsed by a majority of Panel members. Updates to existing sections that do not affect the rated recommendations are approved by Panel cochairs without a Panel vote. Panel members are required to keep all Panel deliberations and unpublished data considered during the development of the Guidelines confidential.

Method of Synthesizing Data and Formulating Recommendations

The working groups critically review and synthesize the available data to develop recommendations. Aspects of the data that are considered include, but are not limited to, the source of the data, the type of study (e.g., case series, prospective or retrospective cohorts, 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 **B:** Moderate recommendation for the statement **C:** Optional recommendation for the statement	**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

It is important to note that, at present, to develop the recommendations in these Guidelines, the Panel incorporates data from the rapidly growing published scientific literature on COVID-19. The Panel also relies heavily on experience with other diseases, supplemented with evolving personal clinical experience with COVID-19.

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

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

Evolving Knowledge on Treatment for COVID-19

Currently, 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 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 (EUAs), Emergency Investigational New Drug (EIND) applications, compassionate use or expanded access programs with drug manufacturers, and/or off-label use.

Whenever possible, the Panel recommends that promising, unapproved, or unlicensed treatments for COVID-19 be studied in well-designed, controlled clinical trials. This 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.

A large volume of data and publications from randomized controlled trials, observational cohorts, and case series are emerging at a very rapid pace, some in peer-reviewed journals, others as pre-peer-review manuscripts, and, in some cases, press releases. The Panel continuously reviews the available data and assesses their scientific rigor and validity. These sources of data and the experiences of the Panel members are used to determine whether new recommendations or changes to the current recommendations are warranted.

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

Overview of COVID-19: Epidemiology, Clinical Presentation, and Transmission

Last Updated: July 17, 2020

Epidemiology

The COVID-19 pandemic has exploded since cases were first reported in China in December 2019. As of July 9, 2020, more than 12 million cases of COVID-19—caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection—have been reported globally, including more than 550,000 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 serious COVID-19 disease is higher in people aged ≥60 years, those living in a nursing home or long-term care facility, and those with chronic medical conditions. In a recent analysis of more than 1.3 million laboratory-confirmed cases that were reported in the United States between January and May 2020, 14% of patients required hospitalization, 2% were admitted to the intensive care unit, and 5% died.[3] The percentage of patients who died was 12 times higher (19.5% vs. 1.6%) and the percentage of patients who were hospitalized was six times higher (45.4% vs. 7.6%) in those with reported medical conditions than in those without medical conditions. The mortality rate was highest in those aged >70 years, regardless of chronic medical conditions. Among those with available data on health conditions, 32% had cardiovascular disease, 30% had diabetes, and 18% had chronic lung disease. Other conditions that may lead to a high risk for severe COVID-19 include cancer, kidney disease, obesity, sickle cell disease, transplant recipients, and other immunocompromising conditions.[2,4-9]

Emerging data from the United States suggest that racial and ethnic minorities experience higher rates of COVID-19 and subsequent hospitalization and death.[10-14] However, surveillance data that include race and ethnicity are not available for most reported cases of COVID-19 in the United States.[2,15] Factors that contribute to the increased burden of COVID-19 in these populations may include over-representation in work environments that confer higher risks of exposure to COVID-19, economic inequality (which limits a person's ability to protect against COVID-19 exposure), neighborhood disadvantage,[16] and a lack of access to health care.[15] Structural inequalities in society contribute to health disparities for racial and ethnic minority groups, including higher rates of comorbid conditions (e.g., cardiac disease, diabetes, hypertension, obesity, pulmonary diseases), which further increases the risk for severe illness from COVID-19.[14]

Clinical Presentation

The estimated incubation period for COVID-19 is up to 14 days from the time of exposure, with a median incubation period of 4 to 5 days.[6,17,18] The spectrum of illness can range from asymptomatic infection to severe pneumonia with acute respiratory distress syndrome (ARDS) and death. Among 72,314 persons with COVID-19 in China, 81% of cases were reported to be mild (defined in this study as no pneumonia or mild pneumonia), 14% were severe (defined as dyspnea, respiratory frequency ≥30 breaths/min, SpO_2 ≤93%, PaO_2/FiO_2 <300 mmHg, and/or lung infiltrates >50% within 24 to 48 hours), and 5% were critical (defined as respiratory failure, septic shock, and/or multiple organ dysfunction or failure).[19] In a report on more than 370,000 confirmed COVID-19 cases with reported symptoms in the United States, 70% of patients experienced fever, cough, or shortness of breath, 36% had muscle aches, and 34% reported headaches.[3] Other reported symptoms have included, but are not limited to, diarrhea, dizziness, rhinorrhea, anosmia, dysgeusia, sore throat, abdominal pain, anorexia, and vomiting.

The abnormalities seen in chest X-rays vary, but bilateral multi-focal opacities are the most common. The abnormalities seen in computed tomography (CT) of the chest also vary, but the most common are bilateral peripheral ground-glass opacities, with areas of consolidation developing later in the clinical course.[20] Imaging may be normal early in infection and can be abnormal in the absence of symptoms.[20]

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

While COVID-19 is primarily a pulmonary disease, emerging data suggest that it also leads to cardiac,[21,22] dermatologic,[23] hematological,[24] hepatic,[25] neurological,[26,27] renal,[28,29] and other complications. Thromboembolic events also occur in patients with COVID-19, with the highest risk in critically ill patients.[30] The long-term sequelae of COVID-19 survivors are currently unknown.

Recently, SARS-CoV-2 has been associated with a potentially severe inflammatory syndrome in children (multisystem inflammatory syndrome in children or MIS-C).[31,32] Please see Special Considerations in Children for more information.

Routes of SARS-CoV-2 Transmission

Transmission of SARS-CoV-2 occurs primarily through respiratory secretions, and, to a lesser extent, contact with contaminated surfaces. Most transmissions are thought to occur through droplets; covering coughs and sneezes and maintaining a distance of six feet from others can reduce the risk of transmission. When consistent distancing is not possible, face coverings may further reduce the spread of droplets from infectious individuals to others. Frequent handwashing is also effective in reducing acquisition.[33] The onset and duration of viral shedding and the period of infectiousness are not completely defined. Viral RNA may be detected in upper respiratory specimens from asymptomatic or pre-symptomatic individuals with SARS-CoV-2.[34] An increasing number of studies have described cases where asymptomatic individuals have transmitted SARS-CoV-2.[35-37] The extent to which this occurs remains unknown, but this type of transmission may be contributing to a substantial amount of community transmission.

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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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Prevention and Prophylaxis of SARS-CoV-2 Infection

Last Updated: July 17, 2020

Summary Recommendations
• The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of any agents for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pre-exposure prophylaxis (PrEP), except in a clinical trial **(AIII)**. • The Panel **recommends against** the use of any agents for SARS-CoV-2 post-exposure prophylaxis (PEP), except in a clinical trial **(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

General Prevention Measures

Most transmissions of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are thought to occur through respiratory droplets, and the risk of transmission can be reduced by covering coughs and sneezes and maintaining a distance of at least 6 feet from others. When consistent distancing is not possible, face coverings may further reduce the spread of droplets from infectious individuals to others. Frequent handwashing is also effective in reducing the risk of acquisition.[1] Health care providers should follow the Centers for Disease Control and Prevention (CDC) recommendations for infection control and appropriate use of personal protective equipment.[2]

Vaccines

Vaccines for SARS-CoV-2 are aggressively being pursued. Vaccine development is typically a lengthy process, often requiring multiple candidates before one proves to be safe and effective. To address the current pandemic, several platforms are being used to develop candidate vaccines for Phase 1/2 trials; those that show promise are rapidly moving into Phase 3 trials. Several standard platforms, such as inactivated vaccines, live-attenuated vaccines, and protein subunit vaccines, are being pursued. Some novel approaches are being investigated, including DNA-based and RNA-based strategies and replicating and nonreplicating vector strategies, with the hope of identifying a safe and effective vaccine that can be used in the near future.[3,4]

Pre-Exposure Prophylaxis

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

Rationale

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

Post-Exposure Prophylaxis

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

Rationale

At present, no known agent can prevent SARS-CoV-2 infection after exposure (i.e., as PEP). Potential options for PEP that are currently under investigation include chloroquine, hydroxychloroquine, lopinavir/ritonavir, nitazoxanide, vitamin super B-complex, and vitamin D. Other strategies that are in development include the use of SARS-CoV-2 monoclonal antibodies and convalescent plasma. Please check ClinicalTrials.gov for the latest information.

Clinical Trial Data

Both chloroquine and hydroxychloroquine have *in vitro* activity against SARS-CoV and SARS-CoV-2.[5,6] A small cohort study without a control group has suggested that hydroxychloroquine might reduce the risk of household transmission.[7]

A randomized, double-blind, controlled trial enrolled 821 participants using an internet-based survey. Study participants had either high or moderate risk of occupational exposures (66% of participants) or household exposures (34% of participants). High-risk exposure was defined as being within 6 feet of an individual with confirmed SARS-CoV-2 infection for more than 10 minutes while not wearing a face mask or eye shield (87.6% of participants), and moderate-risk exposure was defined as the same exposure while wearing a face mask but no eye shield (12.4% of participants).[8]

Participants were randomized to receive placebo or hydroxychloroquine sulfate given once at a relatively high dose of 800 mg, followed by 600 mg 6 to 8 hours later, then 600 mg once daily for 4 additional days. Because enrollment was done online, study drugs were sent by overnight mail, resulting in more than 50% of participants initiating their first dose 3 to 4 days after exposure to SARS-CoV-2.[8]

A total of 107 participants had a primary outcome of symptomatic illness, with SARS-CoV-2 infection confirmed by molecular test or by the development of a compatible, COVID-19-related syndrome based on CDC criteria. Due to limited access to molecular diagnostic testing, confirmation of infection occurred for only 16 of the 107 participants (15%). There was no statistically significant difference between the incidences of a primary outcome in the hydroxychloroquine and placebo groups (11.8% vs. 14.3%, respectively; $P = 0.35$). There were more adverse events in the hydroxychloroquine group; mostly nausea, loose stools, and abdominal discomfort, with no serious adverse reactions or cardiac arrhythmias.[8]

This study had several important limitations, including:

- Initiation of therapy was delayed for at least 3 days after exposure to SARS-CoV-2 in the majority of participants.
- Only 15% of participants who reached the primary outcome had SARS-CoV-2 infection confirmed by molecular diagnostics.
- The study population was young (with a median age of 40 years) and consisted of participants who had a relatively low risk of severe COVID-19.

It is notable that while high doses of hydroxychloroquine were associated with an increase in the frequency of adverse events, the reported adverse events were mostly mild, with no serious events reported.

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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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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: July 17, 2020

Comorbid Conditions

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

As is the case for 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 comorbidities 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 procedures that require 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, empiric broad-spectrum antimicrobial therapy is the 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 extrapulmonary 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.

Thromboembolic Events and COVID-19

Critically ill patients with COVID-19 have been observed to have a prothrombotic state, which is characterized by the elevation of certain biomarkers and an apparent increase in the incidence of venous thromboembolic disease. In some studies, thromboemboli have been diagnosed in patients who received chemical prophylaxis with heparinoids.[12-14] Autopsy studies provide additional evidence of both thromboembolic disease and microvascular thrombosis in patients with COVID-19.[15] Some authors have called for routine surveillance of ICU patients for venous thromboembolism.[16] Please refer to Antithrombotic Therapy for a more detailed discussion.

Renal and Hepatic Dysfunction Due to COVID-19

Although severe acute respiratory syndrome coronavirus 2 (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 case series.[5] See Acute Kidney Injury and Renal Replacement Therapy for a more detailed discussion.

Special Considerations in Children

Several large, epidemiologic studies suggest that rates of ICU admission are substantially lower for children with COVID-19 than for adults. However, severe disease does occur in children.[17-22] The risk factors for severe COVID-19 disease in children have not yet been established. Based on data from studies of adults and extrapolation from data on other pediatric respiratory viruses, severely immunocompromised children and those with underlying cardiopulmonary disease may be at higher risk for severe disease.

A new syndrome, multisystem inflammatory syndrome in children (MIS-C), which appears to be a postinfectious complication, has been described.[23,24] Certain symptoms of MIS-C often require ICU-level care, including blood pressure and inotropic support. These symptoms include severe abdominal pain, multisystem inflammation, shock, cardiac dysfunction, and, rarely, coronary artery aneurysms. A minority of children with MIS-C meet criteria for typical or atypical Kawasaki disease. For details on MIS-C clinical features and the treatments that are being investigated, see Special Considerations in Children.

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

All ICU patients should be routinely monitored for drug-drug interactions. The potential for drug-drug interactions between investigational 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. When treating patients with COVID-19, clinicians also need to minimize the risk of 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 comorbid conditions.[25,26]

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.[27] 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: July 17, 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 either conventional oxygen therapy (hazard ratio [HR] 2.01; 95% confidence interval [CI], 1.01–3.99) or NIPPV (HR 2.50; 95% CI, 1.31–4.78).[8]

In the subgroup of more severely hypoxemic patients with $PaO_2/FiO_2 \leq 200$, 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 after 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 computed 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 maintaining their improved oxygen saturation after 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 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

PEEP is beneficial in patients with ARDS because it prevents alveolar collapse, improves oxygenation, and minimizes atelectotrauma, a source of ventilator-induced lung injury. A meta-analysis of individual patient data from the three largest trials that compared lower and higher levels of PEEP found lower rates of ICU mortality and in-hospital mortality with higher PEEP in patients with moderate (P/F ratio of 100–200) and severe ARDS (P/F ratio <100).[29]

Though there is no clear standard as to what constitutes a high level PEEP, one conventional threshold is >10 cm H_2O.[30] Recent reports have suggested that, in contrast to other causes of ARDS, some patients with moderate or severe ARDS due to COVID-19 have normal static compliance; higher PEEP levels may cause harm in this group by compromising hemodynamics and cardiovascular performance.[31,32] However, this finding has not been confirmed in other studies. Several observational studies reported that patients with moderate to severe ARDS due to COVID-19 had low compliance, similar to the lung compliance seen in patients with conventional ARDS.[33-36] In patients with ARDS due to COVID-19, assessment for responsiveness to higher PEEP may be individualized based on oxygenation and lung compliance. Clinicians should monitor patients for known side effects of higher PEEP, such as

barotrauma and hypotension.

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-induced 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 personal protective equipment 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 Corticosteroids (Including 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: July 17, 2020

Summary Recommendations

There are no Food and Drug Administration-approved drugs for the treatment of COVID-19. Definitive clinical trial data are needed to identify safe and effective treatments for COVID-19. In this table, the COVID-19 Treatment Guidelines Panel (the Panel) provides recommendations for using antiviral drugs to treat COVID-19 based on the available data. **As in the management of any disease, treatment decisions ultimately reside with the patient and their health care provider.**

For more information on 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

- In situations where remdesivir supplies are limited, the Panel recommends that **remdesivir** be prioritized for use in hospitalized patients with COVID-19 who require supplemental oxygen but who are not mechanically ventilated or on extracorporeal membrane oxygenation (ECMO) **(BI)**.

The following recommendation statements for the use of remdesivir are currently being revised and will be updated soon:

- The Panel recommends administering the investigational antiviral agent **remdesivir** for 5 days for the 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 the treatment of COVID-19 in patients who are on mechanical ventilation or ECMO **(BI)**.

Recommendation for Duration of Therapy for Patients Who Have Not Shown Substantial Clinical Improvement After 5 Days of Therapy

- There are insufficient data on the optimal duration of therapy for patients who have not shown substantial clinical 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 either for or against the use of **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)**.
- 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

Antiviral Therapy

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

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

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Remdesivir

Last Updated: July 24, 2020

Remdesivir is an intravenous (IV) investigational nucleotide prodrug of an adenosine analog. Remdesivir binds to the viral RNA-dependent RNA polymerase, inhibiting viral replication through premature termination of RNA transcription. It has demonstrated *in vitro* activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] In a rhesus macaque model of SARS-CoV-2 infection, remdesivir treatment was initiated soon after inoculation; remdesivir-treated animals had lower virus levels in the lungs and less lung damage than the control animals.[2]

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

Recommendation for Prioritizing Limited Supplies of Remdesivir

- **Because remdesivir supplies are limited, the Panel recommends that remdesivir be prioritized for use in hospitalized patients with COVID-19 who require supplemental oxygen but who are not on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) (BI).**

In this section, "high-flow oxygen" refers to the receipt of supplemental oxygen through a high-flow device.

Recommendation for Patients with Mild or Moderate COVID-19

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

Recommendation for Patients with COVID-19 Who Are on Supplemental Oxygen but Who Do Not Require High-Flow Oxygen, Noninvasive or Invasive Mechanical Ventilation, or ECMO

- The Panel recommends using **remdesivir** for 5 days or until hospital discharge, whichever comes first **(AI)**.
- If a patient who is on supplemental oxygen while receiving remdesivir progresses to requiring high-flow oxygen, noninvasive or invasive mechanical ventilation, or ECMO, the course of remdesivir should be completed.

Recommendation for Patients with COVID-19 Who Require High-Flow Oxygen, Noninvasive Ventilation, Mechanical Ventilation, or ECMO

- Because there is uncertainty regarding whether starting remdesivir confers clinical benefit in these groups of patients, the Panel cannot make a recommendation either for or against starting remdesivir.

In a randomized clinical trial, there was no observed difference between the remdesivir and placebo groups in time to recovery or mortality rate in these subgroups. However, because the trial was not powered to detect differences in outcomes in these subgroups, there is uncertainty as to the effect of remdesivir on the course of COVID-19 in these patients.

Duration of Therapy for Patients Who Have Not Shown Clinical Improvement After 5 Days of Therapy

- There are insufficient data on the optimal duration of remdesivir therapy for patients with COVID-19 who have not shown clinical improvement after 5 days of therapy. In this group, some

experts extend the total remdesivir treatment duration to up to 10 days **(CIII)**.

Rationale

The recommendations for remdesivir are largely based on data from a multinational, randomized, placebo-controlled trial (the Adaptive COVID-19 Treatment Trial [ACTT]). This trial included 1,063 hospitalized patients with COVID-19 and evidence of lower respiratory tract infection who received IV remdesivir or placebo for 10 days (or until hospital discharge, whichever came first).

Participants who received remdesivir had a shorter time to clinical recovery than those who received placebo (median recovery time of 11 days vs. 15 days, respectively).[3] In the preliminary subgroup analyses of ACTT, there was no observed benefit for remdesivir in people with COVID-19 who did not require oxygen supplementation; 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 preliminary analysis also reported that the patients with the clearest evidence of clinical benefit from starting remdesivir were those who required supplemental oxygen but who did not require high-flow oxygen, noninvasive or mechanical ventilation, or ECMO at baseline (n = 421). In this subgroup, those who received remdesivir had a shorter time to recovery than those who received placebo (recovery rate ratio 1.47; 95% confidence interval [CI], 1.17–1.84); in a post-hoc analysis of deaths by Day 14, remdesivir appeared to confer a survival benefit (hazard ratio [HR] for death 0.22; 95% CI, 0.08–0.58).

In patients who required high-flow oxygen or noninvasive ventilation at baseline (n = 197), there was no observed difference in time to recovery between the remdesivir and placebo groups (recovery rate ratio 1.20; 95% CI, 0.79–1.81). In the post-hoc analysis of deaths by Day 14, there was no evidence that remdesivir had an impact on the mortality rate in this subgroup (HR 1.12; 95% CI, 0.53–2.38).

In participants who were on mechanical ventilation or ECMO at baseline (n = 272), there was no observed difference in time to recovery between the remdesivir and placebo groups (recovery rate ratio 0.95; 95% CI, 0.64–1.42). In the post-hoc analysis of deaths by Day 14, there was no evidence that remdesivir had an impact on the mortality rate in this subgroup (HR 1.06; 95% CI, 0.59–1.92).

A review of the final data set, which included 28-day mortality, showed that this data set was consistent with the published preliminary data (unpublished data, based on communication from the ACTT study team to the Panel).

For patients with COVID-19 who required high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO, there was no observed difference between the remdesivir and placebo groups in time to recovery or mortality rate. However, because the trial was not powered to detect differences in outcomes within these subgroups, there is uncertainty as to whether starting remdesivir confers clinical benefit in these patients. For this reason, the Panel cannot make a recommendation either for or against starting remdesivir in these patients. Because the supply of remdesivir is limited, the Panel recommends that the drug be prioritized for use in those in whom efficacy has been demonstrated (i.e., in hospitalized patients who require supplemental oxygen but who are not on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO).

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.[4] The optimal duration of therapy for patients who do not improve after 5 days of receiving remdesivir is unclear. In the absence of data, some experts consider extending the total treatment duration of remdesivir to up to 10 days in patients who do not improve after 5 days of remdesivir.[5]

Clinical Data to Date

Multinational Randomized Controlled Trial of Remdesivir Versus Placebo in Hospitalized Patients

ACTT is a National Institutes of Health-sponsored, multinational, randomized, double-blind, placebo-controlled trial in hospitalized adults with COVID-19.[3] 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 eight-point 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 room 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) of <30 mL/min, and those who were pregnant or breastfeeding.

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 comorbidities; 37% were obese (the mean body mass index was 30.6 kg/m^2).
- 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.
- At the time of this preliminary analysis, 132 remdesivir recipients and 169 placebo recipients had not recovered and had not completed the Day 29 follow-up visit.

Preliminary Analyses

- Remdesivir significantly reduced time to recovery compared to placebo (the median time to recovery was 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 outlined above was significantly higher at Day 15 in patients who received remdesivir than in those who received placebo (odds ratio 1.50; 95% CI, 1.18–1.91; $P < 0.001$).
- The benefit of remdesivir for reducing time to recovery was clearest in the subgroup of hospitalized patients who required supplemental oxygenation at study enrollment (ordinal scale 5, n = 421; recovery rate ratio 1.47; 95% CI, 1.17–1.84). In a post-hoc analysis of deaths by Day 14, remdesivir appeared to confer a survival benefit in this subgroup (HR for death 0.22; 95% CI 0.08–0.58).
- In patients who required high-flow oxygen or noninvasive ventilation at study enrollment (ordinal scale 6, n = 197), there was no observed difference between the remdesivir and placebo groups in time to recovery (recovery rate ratio 1.20; 95% CI, 0.79–1.81). In a post-hoc analysis of deaths by Day 14, there was no evidence that remdesivir had an impact on the mortality rate in this subgroup (HR 1.12; 95% CI, 0.53–2.38).
- Among patients who were on mechanical ventilation or ECMO at study enrollment (ordinal scale 7, n = 272), there was no observed difference in time to recovery between the remdesivir and placebo groups (recovery rate ratio 0.95; 95% CI, 0.64–1.42). In a post-hoc analysis of deaths by Day 14, there was no evidence that remdesivir had an impact on the mortality rate in this subgroup (HR 1.06; 95% CI, 0.59–1.92).
- 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 (n = 119; recovery rate ratio 1.09; 95% CI, 0.73–1.62). Mild to moderate disease was defined as SpO_2 >94% on room air and a respiratory rate of <24 breaths/min 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 (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 data set 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 only required supplemental oxygen. There was no observed benefit of remdesivir in those who were on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO, but the study was not powered to detect differences within subgroups. 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

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:[4]

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 room 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.

Participant characteristics

- Of 402 randomized participants, 397 began 5 days (n = 200) or 10 days (n = 197) of remdesivir treatment.
- The median age, demographic characteristics, and frequency of coexisting conditions were similar between the two 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 ($P = 0.02$).
- 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 participants (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 duration of hospitalization among patients who were discharged on or before Day 14 was 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 status 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

This was a multicenter, double-blind, randomized, placebo-controlled trial that evaluated patients with severe COVID-19 in China.[6] Patients were randomized 2:1 to receive IV remdesivir or normal saline placebo for 10 days. Concomitant use of lopinavir/ritonavir, corticosteroids, and interferons was 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. These patients had SpO_2 ≤94% on room air or PaO_2/FiO_2 <300 mm Hg and radiographically confirmed pneumonia.

Results

- 237 hospitalized patients were enrolled and randomized to treatment from February 6 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 for the remdesivir group and 10 days for 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, a 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 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 between 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 (i.e., corticosteroids, lopinavir/ritonavir, interferons) 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.[7]

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 an increase in prothrombin time (without a change in the international normalized ratio).

Clinical drug-drug interaction studies of remdesivir have not been conducted. Remdesivir levels are unlikely to be substantially altered by cytochrome P450 (CYP) 2C8, CYP2D6, or CYP3A4 enzymes, or by P-glycoprotein (P-gp) or organic anion-transporting polypeptide (OATP) drug transporters.

Remdesivir may be administered with weak to moderate inducers or with strong inhibitors of CYP450, OATP, or P-gp. Strong induction may modestly reduce remdesivir levels. The clinical relevance of lower remdesivir levels is unknown.8 Based on information provided by Gilead (written communication, July 2020), the use of remdesivir with strong inducers (e.g., rifampin) **is not recommended**.

Minimal to no reduction in remdesivir exposure is expected when remdesivir is coadministered with dexamethasone, according to information provided by Gilead (written communication, July 2020). Chloroquine or hydroxychloroquine may decrease the antiviral activity of remdesivir; coadministration of these drugs **is not recommended**.[9]

Because the remdesivir formulation contains renally cleared sulfobutylether-beta-cyclodextrin sodium, patients with an eGFR of <50 mL/min are excluded from some clinical trials (some trials have an eGFR cutoff of <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.[5]
- The safety and effectiveness of remdesivir for treatment of COVID-19 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 Food and Drug Administration (FDA) Emergency Use Authorization (EUA) for adults and children and through compassionate use programs for pregnant women and children with COVID-19.
- Ninety-eight female participants received remdesivir as part of a randomized controlled trial for the treatment of Ebola virus infection; six of these participants had a positive pregnancy test. The obstetric and neonatal outcomes were not reported in the study.[10]

Considerations in Children

- The safety and effectiveness of remdesivir for treatment of COVID-19 have not been evaluated in pediatric patients.

- Remdesivir is available through an FDA EUA for adults and children and through compassionate use programs for children with COVID-19. A clinical trial is currently evaluating the pharmacokinetics of remdesivir in children (*ClinicalTrials.gov* identifier NCT04431453).
- In the same randomized controlled trial for the treatment of Ebola virus infection discussed above, 41 pediatric patients received remdesivir. These patients included neonates and children aged <18 years.[10] The safety and clinical outcomes for children were not reported separately in the published results for the trial.[11]

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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: July 17, 2020

Recommendation

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

Rationale

Chloroquine and hydroxychloroquine have been evaluated for the treatment of COVID-19 in small, randomized clinical trials, case series, and observational studies. 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 Patients With COVID-19

Please also see Chloroquine or Hydroxychloroquine, as that section includes studies in which some of the patients received azithromycin as part of their treatment.

New York Department of Health Study on Hydroxychloroquine With or Without Azithromycin

A retrospective, multicenter, observational study in New York evaluated the use of hydroxychloroquine with and without azithromycin in a random sample of 1,438 inpatients with COVID-19. Patients were categorized into four treatment groups: hydroxychloroquine plus azithromycin, hydroxychloroquine alone, azithromycin alone, or neither drug. The primary outcome measure was in-hospital mortality, and the secondary outcome measure was cardiac arrest and arrhythmia or QT prolongation on an electrocardiogram.[2]

Results

- Patients in the three treatment groups had more severe disease at baseline than those who received neither drug.
- In adjusted analyses, patients who received one of the three treatment regimens did not show a decreased in-hospital mortality rate when compared with those who received neither drug.
- Patients who received hydroxychloroquine plus azithromycin had a greater risk of cardiac arrest than patients who received neither drug (odds ratio 2.13; 95% confidence interval, 1.12–4.05).

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

Despite the limitations discussed above, these findings suggest that although hydroxychloroquine and azithromycin are not associated with an increased risk of in-hospital death, the combination of hydroxychloroquine and azithromycin may be associated with an increased risk of cardiac arrest.

Case Series of Hydroxychloroquine Plus Azithromycin

In a case series of 80 hospitalized patients with COVID-19 (including six patients from a previous study), 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. The mean time from symptom onset to treatment was about 5 days. Study outcomes 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 as determined by polymerase chain reaction (PCR) and SARS-CoV-2 culture (in a convenience sample of patients), and length of stay in the infectious diseases ward.[3]

Clinical Results

- One patient (1.2%) died, three patients (3.8%) required ICU transfer, and 12 patients (15%) required oxygen therapy.
- Sixty-five patients (81.2%) were discharged to home or transferred to other units for continued treatment; 14 patients (17.4%) were still hospitalized when 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

- This trial lacked a control group, which is particularly important because many people with mild disease improve in the absence of treatment.
- This trial lacked complete or longer-term follow-up.

Interpretation

The multiple issues with the trial design and the lack of a control group limit the usefulness of this study for informing recommendations.

Small Prospective Case Series of Hydroxychloroquine Plus Azithromycin

A prospective case series from France assessed 11 consecutive hospitalized patients with COVID-19.[4]

Results

- Eight of the 11 patients had significant comorbid conditions: obesity (in two patients), solid cancer (in three patients), hematological cancer (in two patients), and HIV infection (in one patient).
- Ten of the 11 patients were receiving supplemental oxygen at 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.
- Hydroxychloroquine 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 case series only included 11 patients.

Interpretation

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

Adverse Effects

Multiple reports demonstrate that concomitant use of hydroxychloroquine and azithromycin can prolong QTc; in an observational study, hydroxychloroquine plus azithromycin was associated with increased odds of cardiac arrest.[5-7] The use of this combination warrants careful monitoring.

Please see Chloroquine or Hydroxychloroquine for further details regarding these drugs, including adverse effects, drug interactions, considerations in pregnant people and children, and availability.

Clinical Trials

Clinical trials that are testing the safety and efficacy of chloroquine or hydroxychloroquine with or without azithromycin in people who have or who 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: July 17, 2020

Recommendation

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

Rationale

The pharmacodynamics of HIV protease inhibitors raise concerns about whether it is possible to achieve drug concentrations that can inhibit the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) protease. In addition, lopinavir/ritonavir did not show efficacy in a small randomized controlled trial in patients with COVID-19 (see below).

Lopinavir/Ritonavir

Proposed Mechanism of Action and Rationale for Use in Patients With 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 vitro*, and this protease appears to be highly conserved in SARS-CoV-2.[2,3]
- Although lopinavir/ritonavir has *in vitro* 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; therefore, coronavirus-infected enterocytes might be exposed to higher concentrations of the drug.[5]

Lopinavir/Ritonavir Pharmacokinetics in Patients With COVID-19

In a case series, eight patients with COVID-19 were treated with lopinavir 400 mg/ritonavir 100 mg orally twice daily and had plasma trough levels of lopinavir drawn and assayed by liquid chromatography-tandem mass spectrometry.[6]

Study Results

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

Limitations

- Only the trough levels of lopinavir were quantified.
- No data are available on effective lopinavir concentrations for SARS-CoV-2 *in vivo*.

Interpretation

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

Randomized Controlled Trial of Lopinavir/Ritonavir Versus Standard of Care for COVID-19

In a clinical trial that randomized 199 patients to receive lopinavir 400 mg/ritonavir 100 mg orally twice daily for 14 days or standard of care (SOC), patients who were randomized to the lopinavir/ritonavir arm did not have a shorter time to clinical improvement.[7]

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 a shorter median intensive care unit stay for those in the lopinavir/ritonavir group than those in the SOC group (6 days vs. 11 days; difference of -5 days; 95% confidence interval, -9 to 0 days).
- 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.

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 SOC.

Lopinavir/Ritonavir Plus Interferon Beta-1b Plus Ribavirin for COVID-19

Also see Interferons for a description of this trial and its results.

An open-label, Phase 2 clinical trial randomized 127 participants with COVID-19 2:1 to receive either a 14-day course of a combination therapy that included interferon beta-1b 8 million international units administered subcutaneously on alternating days (1–3 doses, depending on time from symptom onset) plus lopinavir 400 mg/ritonavir 100 mg orally every 12 hours and ribavirin 400 mg orally every 12 hours, or a 14-day course of lopinavir 400 mg/ritonavir 100 mg every 12 hours alone.

In the combination therapy group, those who were admitted <7 days after symptom onset (n = 52) received triple-drug therapy; however, interferon beta-1b was not included in the regimen for those who were admitted ≥7 days after symptom onset (n = 34) because of concerns regarding its potential for inflammatory effects. The study population consisted of patients who were hospitalized in Hong Kong; the median age was 52 years and the median time from symptom onset to enrollment was 5 days. Only 12% to 14% of participants were on supplemental oxygen, and only one participant was mechanically ventilated.[8]

Study Results

- Patients in the combination therapy group showed faster viral clearance and more rapid clinical improvement than those in the control group.
- See the Interferons section for additional data.

Limitations

- Participants in both arms received lopinavir/ritonavir, so it is impossible to determine whether lopinavir/ritonavir contributed to the observed treatment effects. However, the possibility that lopinavir/ritonavir may have contributed to the effectiveness of the combination therapy also cannot be ruled out.

- The positive clinical impact of the combination therapy was limited to those who were hospitalized <7 days from symptom onset.
- Most participants in this study had mild illness: only slightly more than 10% were on supplemental oxygen. For this reason, the study has limited applicability to hospitalized patients in the United States.

Interpretation

This study neither supports nor refutes the use of lopinavir/ritonavir with or without ribavirin in patients with COVID-19. See the Interferons section for further discussion.

Lopinavir/Ritonavir Versus Umifenovir Versus Standard of Care

In a trial of 86 hospitalized patients with mild-to-moderate COVID-19, 34 patients were randomized to receive lopinavir/ritonavir, 35 patients received the broad-spectrum antiviral umifenovir (trade name Arbidol; not available in the United States), and 17 patients received SOC.[9]

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

- The time to a negative SARS-CoV-2 nucleic acid pharyngeal swab was similar between the two groups. Patients who received lopinavir/ritonavir achieved a negative SARS-CoV-2 nucleic acid pharyngeal swab at a mean of 9 days (standard deviation [SD] ± 5.0 days) and those who received SOC achieved it at a mean of 9.3 days (SD ± 5.2 days).
- Progression to severe illness occurred among six patients in the lopinavir/ritonavir arm (18%) and two patients who received SOC (12%).
- Two patients became critically ill; both were randomized to receive lopinavir/ritonavir.

Limitations

- The trial had a small sample size.
- The study was not blinded.
- The effectiveness of umifenovir 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 or Hydroxychloroquine section for the study description.[10]

Clinical Trials

Please check *ClinicalTrials.gov* for the latest information.

Monitoring, Adverse Effects, and Drug-Drug Interactions

The adverse effects for lopinavir/ritonavir include:

- Nausea, vomiting, diarrhea (common)
- QTc prolongation
- Hepatotoxicity

Lopinavir/ritonavir is a potent inhibitor of cytochrome P450 3A, and many medications that are

metabolized by this enzyme may cause severe toxicity. Please refer to the Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV for a list of potential drug interactions.

Considerations in Pregnancy

- There is extensive experience with the use of lopinavir/ritonavir in pregnant women with HIV, and the drug has a good safety profile.
- There is no evidence of human teratogenicity (can rule out a 1.5-fold increase in overall birth defects).
- Lopinavir has 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.
- The use of once-daily dosing for lopinavir/ritonavir **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 using lopinavir/ritonavir to treat COVID-19 in pediatric patients.

Darunavir/Cobicistat or Darunavir/Ritonavir

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

- Darunavir inhibits the 3CLpro enzyme of SARS-CoV-2 and possibly also inhibits the PLpro enzyme.
- In an *in vitro* study, darunavir did not show activity against SARS-CoV-2.[11]
- 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.[12]

Clinical Trials

There are currently no clinical trials that are evaluating the use of darunavir/cobicistat or darunavir/ritonavir in participants with COVID-19 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: July 17, 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:** Most studies of COVID-19 use AZM with HCQ.	• Mycobacterial (nontuberculous) infection • STIs and various bacterial infections[1]	• Induction of IFN-stimulated genes, attenuating viral replication[2] • Enhanced neutrophil activation[3] • 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 has primarily been studied for the treatment of COVID-19 in combination with HCQ. The RECOVERY trial includes an AZM monotherapy arm, which is currently enrolling. • Please see the description of the combination therapy study results in the Hydroxychloroquine Plus Azithromycin section below and in Hydroxychloroquine Plus Azithromycin.
Chloroquine	• Malaria • Extra-intestinal amebiasis	• Increases endosomal pH, inhibiting fusion of SARS-CoV-2 and the host cell membranes[4] • Inhibits glycosylation of the cellular ACE2 receptor, which may interfere with binding of SARS-CoV to the cell receptor[5] • May block the transport of SARS-CoV-2 from early endosomes to endolysosomes *in vitro*, which may be required to release the viral genome[6] • Immunomodulatory effects	**High-Dose vs. Low-Dose CQ:**[7] • A randomized, double-blind, Phase 2b study compared 2 different CQ regimens, CQ 600 mg twice daily for 10 days (high dose) vs. CQ 450 mg twice daily for 1 day followed by 450 mg for 4 days (low dose), in hospitalized adults with suspected cases of severe COVID-19 (respiratory rate >24 breaths/min, 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. • 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%]

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date Find clinical trials on ClinicalTrials.gov
Chloroquine, continued			vs. in 6 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 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). • 2 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 a negative SARS-CoV-2 PCR test result at Days 10 and 14. Secondary outcomes included improvement of lung 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:* • 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 comorbidities. • 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; these variables could have affected the study protocol-defined outcomes. • Patients who had chronic comorbidities and who were critically ill were excluded from the study. *Interpretation:* • In this small randomized controlled trial, CQ and LPV/r showed similar efficacy in treating COVID-19.

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date Find clinical trials on ClinicalTrials.gov
Hydroxychloroquine	• Lupus erythematosus • Malaria • Rheumatoid arthritis[9]	• Increases the endosomal pH, inhibiting fusion of SARS-CoV-2 and the host cell membranes[4] • May block the transport of SARS-CoV-2 from early endosomes to endolysosomes *in vitro*, which may be required to release the viral genome[6] • Immunomodulatory effects	**New York Department of Health Study on HCQ With or Without AZM:** • A retrospective, multicenter, observational study in New York evaluated the use of HCQ with and without AZM in a random sample of 1,438 inpatients with COVID-19. Patients were categorized into 4 treatment groups: HCQ plus AZM, HCQ alone, AZM alone, or neither drug. The primary outcome measure was in-hospital mortality, and the secondary outcome measure was cardiac arrest and arrhythmia or QT prolongation on an ECG. *Results:* • Patients in the 3 treatment groups had more severe disease at baseline than those who received neither drug. • In adjusted analyses, patients who received 1 of the 3 treatment regimens did not show a decreased in-hospital mortality rate when compared with those who received neither drug. • Patients who received HCQ plus AZM had a greater risk of cardiac arrest than patients who received neither drug (OR 2.13; 95% CI, 1.12–4.05). *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:* • Despite the limitations discussed above, these findings suggest that although HCQ and AZM are not associated with an increased risk of in-hospital death, the combination of HCQ and AZM may be associated with an increased risk of cardiac arrest. **Observational Study of 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.

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date Find clinical trials on ClinicalTrials.gov
Hydroxychloroquine, continued			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. *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

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date Find clinical trials on ClinicalTrials.gov
Hydroxychloroquine, continued			Veterans Health Administration medical centers between March 9–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 need for mechanical ventilation. Associations between treatment and outcomes were determined using propensity score adjustment, including demographic data, comorbidity data, 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 3 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. • The risk of death from any cause was higher in the HCQ group than in the no HCQ group (adjusted HR 2.61; 95% CI, 1.10–6.17; $P = 0.03$). The no HCQ group and the HCQ plus AZM group had similar risks of death from any cause (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; however, 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; the severity of chest X-ray findings could predict worse outcomes.

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date Find clinical trials on ClinicalTrials.gov
Hydroxychloroquine, continued			• The use of other antiviral or immunomodulatory agents were 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 or moderate disease at admission. *Interpretation:* • This study showed no beneficial effect of HCQ plus AZM for the treatment of COVID-19 and a possible association between the use of HCQ and an increased risk of mortality; however, residual confounding may have affected the study results. **Randomized, Controlled Trial of HCQ vs. SOC for Mild or 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 or moderate COVID-19 [99% of the patients] and 3 weeks for 2 patients with severe disease) and SOC. • The primary outcome was a negative PCR test result 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 levels), 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. • The HCQ arm and the SOC arm had similar negative PCR conversion rates within 28 days (85.4% of participants vs. 81.3% of participants, respectively) and similar times 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) and in 9% of the participants in the SOC arm. *Limitations:* • It is unclear how the overall rate of symptom alleviation was calculated.

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date Find clinical trials on ClinicalTrials.gov
Hydroxychloroquine, continued			• 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. *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 4 French tertiary care centers over a 2-week period (March 17–31, 2020). Patients aged 18–80 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 1 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, 8 received HCQ beyond 48 hours, and 89 did not receive HCQ. • Comorbidities 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 survival rates without ICU transfer at Day 21 between the HCQ group (76% of participants) and the non-HCQ group (75% of participants). Similarly, there was

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

Hydroxychloroquine, continued			no difference between the groups in the secondary outcomes of survival rate and survival rate without ARDS at Day 21.
			• Among the 84 patients who received HCQ within 48 hours, 8 patients (10%) experienced ECG changes that required treatment discontinuation at a median of 4 days from the start of dosing, including 7 patients with a QTc that prolonged >60 ms and 1 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 the rates of 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 either asymptomatic SARS-CoV-2 infection or upper or lower respiratory tract infection received HCQ 200 mg 3 times daily for 10 days. These patients were compared to 16 control individuals (i.e., those who refused treatment, did not meet eligibility criteria, or were from a different clinic).
			Results:
			• 6 patients in the HCQ group were excluded from the analysis for the following reasons:
			  • 1 patient died,
			  • 3 patients were transferred to the ICU,
			  • 1 patient stopped the study drug due to nausea, *and*
			  • 1 patient withdrew from the study.
			• 6 patients also received AZM.
			• By Day 6, NP PCRs were negative in 14 of 20 HCQ-treated patients (70%) and 2 of 16 controls (12.5%).
			• Among the HCQ patients, 8 of 14 (57.1%) who received only HCQ and 6 of 6 (100%) who received HCQ and AZM had negative NP PCRs by Day 6.
			• Clinical outcomes were not reported for all patients.

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date Find clinical trials on ClinicalTrials.gov
Hydroxychloroquine, continued			*Limitations:* • The sample size of the series is small. • The criteria for enrollment of cases and controls is unclear. • Asymptomatic individuals were enrolled. • Exclusion of 6 HCQ-treated patients includes 1 death and 3 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 and Hydroxychloroquine sections above.	See the Azithromycin and Hydroxychloroquine sections above.	**Case Series of HCQ Plus AZM:**[15] • In a case series of 80 hospitalized patients with COVID-19 (including 6 patients from a previous study),[14] patients were treated with HCQ 200 mg 3 times daily for 10 days plus AZM 500 mg once daily for 1 day followed by AZM 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 as determined 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:* • 1 patient died (1.2%), 3 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:* • SARS-CoV-2 NP 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.

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Hydroxychloroquine Plus Azithromycin, continued			*Limitations:* • The trial lacked a control group, which is particularly important because many people with mild disease improve in the absence of treatment. • The trial lacked complete or longer-term follow-up. *Interpretation:* • The multiple issues with trial design and the lack of a control group limit the usefulness of this study for informing recommendations. **Small Prospective Case Series of HCQ Plus AZM:**[16] • A prospective case series from France assessed 11 consecutive hospitalized patients with COVID-19. *Results:* • 8 of the 11 patients had significant comorbid conditions: obesity (n = 2), solid cancer (n = 3), hematological cancer (n = 2), and HIV infection (n = 1). • 10 of 11 patients were receiving supplemental oxygen at 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 AZM 250 mg once daily for 4 days. • Within 5 days, the condition of 3 patients worsened, including 1 patient who died and 2 patients who were transferred to the ICU. • HCQ was discontinued in 1 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 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).

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Hydroxychloroquine Plus Azithromycin, continued			*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. • Some participants were receiving concomitant drugs that had the potential to prolong the QTc interval; 11% of participants were receiving neuropsychiatric drugs and 8% of participants were receiving levofloxacin, LPV/r, or tacrolimus. • 4 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. • 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:* • This was a descriptive case series. *Interpretation:* • This case series demonstrated that HCQ plus AZM can prolong QTc and that the use of this 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]	**LPV/r Pharmacokinetics in Patients With COVID-19:** • In a case series, 8 patients with COVID-19 were treated with LPV/r 400 mg/100 mg orally twice daily and had plasma trough levels of LPV drawn and assayed by liquid chromatography-tandem mass spectrometry.[20] *Results:* • The median plasma LPV concentration was 13.6 µg/mL. • After correcting for protein binding, trough levels would need to be approximately 60-fold to 120-fold higher to achieve the *in vitro* EC_{50} for SARS-CoV-2. *Limitations:* • Only the trough levels of LPV were quantified. • No data are available on effective LPV concentrations for SARS-CoV-2 *in vivo*.

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:* • The plasma drug concentrations that were achieved using typical doses of LPV/r are far below the levels that may be needed to inhibit SARS-CoV-2. **Randomized Controlled Trial of LPV/r vs. SOC:** • In a clinical trial that randomized 199 patients to receive LPV/r 400 mg/100 mg PO twice daily for 14 days or SOC, patients who were 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 a shorter ICU stay for those in the LPV/r group than those in the SOC group (6 days vs. 11 days; difference of -5 days; 95% CI, -9 to 0 days). • 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. *Interpretation:* • A moderate-sized, randomized trial failed to find a virologic or clinical benefit of LPV/r over SOC. **LPV/r Plus IFN Beta-1b Plus Ribavirin for COVID-19:** • Also see Interferons for a description of this trial and its results.

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date Find clinical trials on ClinicalTrials.gov
HIV Protease Inhibitors, continued			• An open-label, Phase 2 clinical trial randomized 127 participants with COVID-19 2:1 to receive either a 14-day course of a combination therapy that included IFN beta-1b 8 million international units administered subcutaneously on alternating days (1–3 doses, depending on time from symptom onset) plus LPV/r 400 mg/100 mg orally every 12 hours and ribavirin 400 mg orally every 12 hours, or a 14-day course of LPV/r 400 mg/100 mg every 12 hours alone.[21] • In the combination therapy group, those who were admitted <7 days after symptom onset (n = 52) received triple-drug therapy; however, IFN beta-1b was not included in the regimen for those who were admitted ≥7 days after symptom onset (n = 34) because of concerns regarding its potential for inflammatory effects. The study population consisted of patients who were hospitalized in Hong Kong; the median age was 52 years and the median time from symptom onset to enrollment was 5 days. Only 12% to 14% of participants were on supplemental oxygen, and only 1 participant was mechanically ventilated. *Results:* • Patients in the combination therapy group showed faster viral clearance and more rapid clinical improvement than those in the control group. *Limitations:* • Participants in both arms received LPV/r, so it is impossible to determine whether LPV/r contributed to the observed treatment effects. However, the possibility that LPV/r may have contributed to the effectiveness of the combination therapy also cannot be ruled out. • The positive clinical impact of the combination therapy was limited to those who were hospitalized <7 days from symptom onset. • Most participants in this study had mild illness, and only slightly more than 10% were on supplemental oxygen. For this reason, the study has limited applicability to hospitalized patients in the United States. *Interpretation:* • This study neither supports nor refutes the use of LPV/r with or without ribavirin in patients with COVID-19. See the Interferons section for further discussion.

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date Find clinical trials on ClinicalTrials.gov
HIV Protease Inhibitors, continued			**LPV/r vs. Umifenovir vs. SOC** • In a trial of 86 hospitalized patients with mild-to-moderate COVID-19, 34 patients were randomized to receive LPV/r, 35 patients received the broad-spectrum antiviral umifenovir (trade name Arbidol; not available in the United States), and 17 patients received SOC.[22] *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 illness occurred among 6 patients (18%) in the LPV/r arm and 2 patients (12%) who received SOC. • 2 patients became critically ill; both were randomized to receive LPV/r. *Limitations:* • The trial had a small sample size. • The study was not blinded. • The effectiveness of umifenovir 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 Chloroquine section above for the study description.
Remdesivir (GS-5734)	• Not approved by FDA	• Binds to the viral RNA-dependent RNA polymerase, inhibiting viral replication through premature termination of RNA transcription • Has demonstrated *in vitro* activity against SARS-CoV-2[4] • In a rhesus macaque model of SARS-CoV-2 infection, RDV treatment was initiated soon after inoculation; RDV-treated animals had lower lung virus levels and less lung damage than the control animals.[23]	**Multinational Randomized Controlled Trial of RDV vs. 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

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Remdesivir, continued			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 1 of the following conditions: • The patient had pulmonary infiltrates, as determined by radiographic imaging, • SpO_2 was ≤94% on room air, • The patient required supplemental oxygen, • The patient 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). • 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 2 or more comorbidities; 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.

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Remdesivir, continued			• 8 RDV recipients and 9 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; recovery rate ratio 1.47; 95% CI, 1.17–1.84). • Among the 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 the patients who were 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 (n = 119; recovery rate ratio 1.09; 95% CI, 0.73–1.62). Mild to moderate disease was defined as SpO_2 >94% and respiratory rate <24 breaths/min 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). • The use of RDV was associated with shorter time to recovery regardless of the 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.

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Remdesivir, continued			*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 7-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 *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 room air or were receiving supplemental oxygen. The study excluded patients who were

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Remdesivir, continued			receiving mechanical ventilation or ECMO or who had multiorgan failure, an ALT or AST level >5 times ULN, or an estimated CrCl <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: 4 patients (2%) were assigned to the 5-day group, and 9 patients (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 2-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 2 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 10-day group (8 days; IQR 5–10 days).

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Remdesivir, continued			• By Day 14, 120 patients (60%) in the 5-day group had been discharged and 16 patients (8%) had died; in the 10-day group, 103 patients (52%) had been discharged and 21 patients (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 was 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. • 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.

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Remdesivir, continued			*Results:* • Between February 6–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; 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 1 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 participants in the RDV group and 68% of participants in the placebo group received corticosteroids. • 28% of participants in the RDV group and 29% of participants in the placebo group received LPV/r. • 29% of participants in the RDV arm and 38% of participants in the placebo arm received IFN 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 2 study arms (14% of participants in the RDV arm vs. 13% in the placebo arm). • 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 2 groups. • The number of participants who experienced AEs was similar between the 2 groups (66% of participants in the RDV arm vs. 64% in the placebo arm).

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date Find clinical trials on ClinicalTrials.gov
Remdesivir, continued			• More participants in the RDV arm discontinued therapy due to AEs (12% of participants in the RDV arm vs. 5% in the placebo arm). *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 (i.e., corticosteroids, LPV/r, IFNs) 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; CrCl = creatinine clearance; CRP = C-reactive protein; CT = computed tomography; DM = diabetes mellitus; DRV/c = darunavir/cobicistat; DSMB = data safety monitoring board; EC_{50} = half-maximal effective concentration; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; eGFR = estimated 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 = lopinavir; 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; RECOVERY = Randomised Evaluation of COVID-19 Therapy; 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: July 17, 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, when 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 **Note:** Most studies of COVID-19 use AZM with HCQ.	AZM 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 ECG and 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:** • CQ 1 gm PO once on Day 1, then 500 mg PO once daily for 4–7 days of total treatment. Treatment duration should be 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 ECG • Follow-up ECG if CQ is given with 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
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:** • HCQ 800 mg PO once on Day 1, then 400 mg PO once daily for 4–7 days of total treatment. Treatment duration should be 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	• CBC, hepatic panel, blood glucose, SCr, potassium, magnesium • Baseline ECG • Follow-up ECG if HCQ is given with QTc-prolonging drugs (e.g., AZM) or if the patient has underlying cardiac disease	• 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 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)**. • Long elimination; half-life is 40–55 days. • Dose-dependent toxicity

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, continued		• 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]			• A list of clinical trials is available here: Hydroxychloroquine
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/m2 plus RTV 75 mg/m^2 (maximum: LPV/r 400 mg/100 mg per dose) PO twice daily for a total of 7 days	• Gastrointestinal effects (e.g., 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 > CYP2D6 substrate • Potent CYP3A4 and CYP2D6 inhibitor • Inducer of UGT1A1 and CYP1A2, CYP2C8, CYP2C9, and CYP2C19	• 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

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 **Note:** RDV 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 the 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 1 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 patients who have not shown adequate improvement after 5 days of therapy. Some experts extend the total RDV treatment duration for up to 10 days **(CIII)**. **Note:** The EUA recommends 10-day therapy for patients on mechanical ventilation or ECMO. **Suggested Dose in EUA[a] for Pediatric Patients Weighing 3.5 to <40 kg** *For Patients Who Require Invasive Mechanical Ventilation and/or ECMO:* • RDV 5 mg/kg mg IV over 30–120 minutes for 1 dose on Day 1, followed by RDV 2.5 mg/kg IV daily over 30–120 minutes on Day 2 through Day 10	• 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. SBECD accumulation may occur in patients with moderate or severe renal impairment. • Gastrointestinal symptoms (e.g., nausea, vomiting)	• Monitor for infusion reactions. • Renal and hepatic function • **Do not administer** RDV if eGFR is <30 mL/min (or if patient is receiving dialysis) or if ALT or AST level is >5 times ULN	• Clinical studies of drug-drug interactions for RDV have not been conducted. • RDV levels are unlikely to be substantially 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. • Strong induction may modestly reduce RDV levels. The clinical relevance of lower RDV levels is unknown. Based on information provided by Gilead (written communication, July 2020), the use of RDV with strong inducers (e.g., rifampin) **is not**	**For Hospitalized Patients With Severe COVID-19:** • In situations where RDV supplies are limited, the Panel recommends that RDV be prioritized for use in hospitalized patients with COVID-19 who require supplemental oxygen but who are not mechanically ventilated or on ECMO **(BI)**. • The following recommendation statements for the use of RDV are currently being revised and will be updated soon: • The Panel recommends administering RDV for 5 days for the treatment of COVID-19 in hospitalized patients with SpO_2 ≤94% on room air (at sea level) or those who require supplemental oxygen **(AI)**, and in patients who are on mechanical ventilation or ECMO **(BI)**. **Recommendation for Duration of Therapy for Patients Who Have Not Shown Substantial Clinical Improvement After 5 Days of Therapy:** • There are insufficient data on the optimal duration of therapy for patients who have

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	*For Patients Who Do Not Require Invasive Mechanical Ventilation and/or ECMO:* • RDV 5 mg/kg mg IV over 30–120 minutes for 1 dose on Day 1, followed by RDV 2.5 mg/kg IV daily over 30–120 minutes on Day 2 through Day 5. If there is no clinical improvement, treatment may be extended for up to 5 additional days (for a total treatment duration of 10 days).			**recommended**. • Minimal to no reduction in RDV exposure is expected when RDV is coadministered with dexamethasone. • CQ or HCQ may decrease the antiviral activity of RDV; coadministration of these drugs **is not recommended**.	not shown substantial clinical improvement after 5 days of therapy. In these groups, some experts extend the total RDV treatment duration to up to 10 days **(CIII)**. **For Patients With Mild or Moderate COVID-19:** • There are insufficient data to recommend either for or against the use of RDV for the treatment of patients with mild or moderate COVID-19. **Availability:** • RDV is available through an EUA[a] 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 room 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; HCQ = hydroxychloroquine; HIV = human immunodeficiency virus; INR = international normalized ratio; IV = intravenous; LPV = lopinavir; LPV/r = lopinavir/ritonavir; OATP = organic anion transporter polypeptide; the Panel = the COVID-19 Treatment Guidelines Panel; P-gp = P-glycoprotein; PI = protease inhibitor; PMA = postmenstrual age; PO = orally; PT = prothrombin time; RDV = remdesivir; RTV = ritonavir; SBECD = sulfobutylether-beta-cyclodextrin sodium; SCr = serum creatinine; UGT = uridine diphosphate glucuronosyltransferase; ULN = upper limit of normal

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

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Given the hyperactive inflammatory effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), agents that modulate the immune response are being explored as adjunctive treatments for the management of moderate to critical COVID-19.[1] These agents include human blood-derived products and immunomodulatory therapies.

Some human blood-derived products are obtained from individuals who have recovered from SARS-CoV-2 infection (e.g., convalescent plasma, immunoglobulin products).[2,3] These heterogenous products are postulated to have either direct antiviral properties, such as with convalescent plasma, and/or immunomodulatory effects like those noted with mesenchymal stem cells.[4] Additionally, neutralizing monoclonal antibodies directed against SARS-CoV-2 have been developed and are under investigation in clinical trials.[5]

Other agents in this group include therapeutics currently approved for the treatment of other immune and/or inflammatory syndromes. These agents include corticosteroids (e.g., glucocorticoids),[6] which as a class possess a broad array of mechanisms to abrogate systemic inflammation, and more targeted anti-inflammatory treatments such as interleukin inhibitors,[7,8] interferons,[9] kinase inhibitors,[10] and others.

In the following sections of the COVID-19 Treatment Guidelines, different blood-derived products and immunomodulators under investigation for the management of COVID-19 are discussed. Items discussed include the proposed rationale for use of these therapies, the clinical safety and efficacy data to date, and the COVID-19 Treatment Guidelines Panel's recommendations for their use.

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Blood-Derived Products Under Evaluation for the Treatment of COVID-19

Last Updated: July 17, 2020

Summary Recommendations

• There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of the following blood-derived products for the treatment of COVID-19:
  • **COVID-19 convalescent plasma**
  • **Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunoglobulins**
• The Panel **recommends against** the use of the following blood-derived products for the treatment of COVID-19, except in a clinical trial:
  • **Mesenchymal stem cells (AII)**
  • **Non-SARS-CoV-2-specific intravenous immunoglobulins (IVIG) (AIII)**. This recommendation should not preclude the use of IVIG when it is otherwise indicated for the treatment of complications that arise during the course of COVID-19.

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

Convalescent Plasma

Last Updated: July 17, 2020

Recommendation:

- There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of **COVID-19 convalescent plasma** for the treatment of COVID-19.

Rationale for Recommendation

Thousands of patients in the United States have received COVID-19 convalescent plasma through clinical trials, expanded access treatment trials, and single-patient Emergency Investigational New Drug (EIND) applications. However, the standards and methods for screening donated plasma for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binding and neutralizing antibodies have not been established. The variability in SARS-CoV-2 antibody levels in donor plasma may have an impact on the efficacy of COVID-19 convalescent plasma products. Clinical data are currently insufficient to evaluate the efficacy of convalescent plasma for the treatment of COVID-19. Safety data from a large, multicenter, expanded access program indicated that uncommon (i.e., in <1% of transfusions) but serious risks of convalescent plasma may include transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), allergic reactions, and death.[1] Another theoretical risk is potential for antibody-dependent enhancement (ADE) of infection.

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

Plasma from donors who have recovered from COVID-19 may contain antibodies to SARS-CoV-2 that may help suppress the virus and modify the inflammatory response.[2]

Clinical Data to Date

Open-Label, Randomized Clinical Trial of Convalescent Plasma in 103 Hospitalized Patients With Severe or Life-Threatening COVID-19

This open-label, randomized clinical trial of convalescent plasma versus standard of care for patients with severe or life-threatening laboratory-confirmed COVID-19 was conducted in seven medical centers in Wuhan, China, from February 14 to April 1, 2020. The primary outcome was time to clinical improvement within 28 days, which was defined as patient discharged alive or a two-point reduction on a six-point disease severity scale. Only plasma units with a SARS-CoV-2 viral spike-receptor binding domain-specific IgG titer of at least 1:640 were transfused. The median dose of ABO-compatible, transfused convalescent plasma was 200 mL. The time from symptom onset to study randomization was 27 days in the treatment group and 30 days in the control group.[3]

Due to control of the COVID-19 outbreak in Wuhan, the trial was terminated early after 103 of the planned 200 patients were enrolled. Among the enrolled patients, 45 had severe disease and 58 had life-threatening disease. Baseline severity scores and use of concomitant therapies were similar between the treatment and control groups. Although the groups were well-balanced by age (with a median age of 70 years in the treatment group vs. 69 years in the control group), the proportion of men in the control group (65%) was greater than in the convalescent plasma group (52%). There was no significant difference between the treatment and control groups in the primary outcome of time to clinical improvement within 28 days (hazard ratio 1.40; 95% confidence interval [CI], 0.79–2.49; P = 0.26). Among those with severe disease, 91% of the convalescent plasma recipients and 68% of the control patients improved by Day 28 (difference 23%; odds ratio [OR] 1.34; 95% CI, 0. 98–1.83; P

= 0.07). Among those with life-threatening disease, 21% of patients in the treatment group and 24% in the control group improved (difference -3.4%; OR 0.86; 95% CI, 0.33–2.24; $P = 0.75$). There was no significant difference in mortality between the groups (16% vs. 24% for the treatment and control groups, respectively; OR 0.65; 95% CI, 0.29–1.46; $P = 0.30$). At 24, 48, and 72 hours, the rates of negative SARS-CoV-2 viral polymerase chain reaction were significantly higher in the convalescent plasma group than in the control group (45% vs. 15%, respectively, at 24 hours, $P = 0.003$; 68% vs. 33%, respectively, at 48 hours, $P = 0.001$; and 87% vs. 38%, respectively, at 72 hours, $P < 0.001$). Two transfusion-related events were reported, including one severe event; both events resolved with supportive care.

Limitations

The limitations of this study include that it was not blind and that, on average, the convalescent plasma was administered approximately 1 month into the disease course. In addition, the study was terminated early, and thus the sample size was insufficient to detect smaller but clinically meaningful differences in clinical outcomes.

Safety Analysis of the First Consecutive 20,000 Patients to Receive Open-Label COVID-19 Convalescent Plasma Through a National Expanded Access Program

The Expanded Access to Convalescent Plasma for the Treatment of Patients with COVID-19 program is an ongoing, open-label, nonrandomized protocol primarily designed to provide adult patients who have severe or life-threatening (critical) COVID-19 with access to convalescent plasma, which is an investigational product in the United States. Secondary objectives are to obtain data on the safety of the intervention. The program is sponsored by the Mayo Clinic and includes a diverse range of clinical sites. Criteria for plasma donors include documented COVID-19, with complete resolution of symptoms for ≥14 days before donation, and either no history of pregnancy or a negative human leukocyte antigen test after a donor's most recent pregnancy. SARS-CoV-2 antibody testing of plasma donors and assessment of SARS-CoV-2 neutralization potential are not mandated. Patients are transfused with 1 or 2 units (200–500 mL) of convalescent plasma. ABO-compatible plasma is used preferentially, but in the absence of ABO-compatible plasma, patients may receive either Group A plasma or low anti-A titer Group O plasma, as available. The main outcomes for the safety analysis are serious adverse events (SAEs), including death; SAEs are reported at 4 hours and at 7 days after transfusion, or as they occur.[4]

The safety analysis describes the first 20,000 plasma recipients, enrolled between April 3 and June 2, 2020. One-third of the participants were aged ≥70 years, 60% were male, and 71% had severe or life-threatening COVID-19. Twenty percent of the participants were African American, 35% were Hispanic/Latino, and 5% were Asian. SAEs within 4 hours of transfusion were reported in 146 (<1%) patients and included 63 deaths. Among the deaths, 13 were determined to be possibly or probably related to the convalescent plasma treatment. The 83 nonfatal SAEs included 37 TACO events, 20 TRALI events, and 26 severe allergic reactions. Life-threatening cardiac events and thrombotic events reported up to 7 days after transfusion included 87 thrombotic/thromboembolic complications, 406 sustained hypotension events, and 643 cardiac events. The overall mortality rate was 8.6% at 7 days. In this study, COVID-19 convalescent plasma therapy was associated with a low incidence (<1%) of serious transfusion-related events.

Limitations

The study design, which does not include a control arm, precludes an assessment of efficacy or the occurrence of ADE of COVID-19.

Retrospective, Single-Center, Case-Control Study Evaluating Convalescent Plasma Plus Standard of Care Versus Standard of Care Without Convalescent Plasma

This study has not been peer reviewed.

This case-control study reports clinical outcomes among 39 consecutive patients who received COVID-19 convalescent plasma through the Food and Drug Administration (FDA) single-patient EIND program while hospitalized at Mount Sinai Hospital in New York City between March 24, 2020, and April 8, 2020. Recipients were transfused with 2 units of ABO-compatible convalescent plasma from donors with a SARS-CoV-2 anti-spike antibody titer of 1:320 dilution. The control group (n = 156) was identified retrospectively from the hospital's electronic health records database. The control patients were hospitalized during the same period as the treated patients, had confirmed COVID-19, did not receive convalescent plasma, and were matched 4:1 to convalescent plasma recipients using propensity scores to correct for measured confounders.[5]

The mean age of the convalescent plasma recipients was 55 years, and 64% of the recipients were male. At the time of transfusion, 34 recipients (87%) required supplemental oxygen (noninvasive), and four recipients (10%) were mechanically ventilated. By Day 14, the clinical condition had worsened in 18% of the convalescent plasma patients and 24% of the control patients ($P = 0.17$). As of May 1, 2020, 13% of the plasma recipients and 24% of the matched control patients had died ($P = 0.04$, log-rank test), and 72% and 67% of the transfused patients and control patients, respectively, had been discharged from the hospital.

Limitations

The study's lack of randomization and the potential for unmeasured patient selection bias limit interpretation of the study results.

Other smaller, uncontrolled case series that describe clinical outcomes in COVID-19 patients have been reported and also suggest that SAEs are uncommon following COVID-19 convalescent plasma treatment.[2,6-11]

Clinical Data for Other Viral Infections

The use of convalescent plasma has been evaluated for other viral diseases, such as SARS, with some suggestion of potential benefit.[12-14] However, no convalescent blood products are currently licensed by the FDA.

Clinical Trials

Randomized clinical trials to evaluate convalescent plasma for the treatment of COVID-19 are underway; a list is available at *ClinicalTrials.gov*.

Drug Availability

The FDA has provided recommendations for the use of COVID-19 convalescent plasma through EIND applications for individual patients and traditional or expanded access IND applications. 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 on that specific program and other trials evaluating convalescent plasma. People who have fully recovered from COVID-19 for ≥2 weeks and who are interested in donating plasma can contact their local blood donor or plasma collection center or refer to the FDA's Donate COVID-19 Plasma website.

Adverse Effects

The risks associated with convalescent plasma transfusion include TRALI, TACO, and allergic transfusion reactions.[8,15] Rare complications include the transmission of infectious pathogens and red cell alloimmunization. There is a theoretical risk of antibody-mediated enhancement of infection.

Considerations in Pregnancy

Several ongoing clinical trials evaluating COVID-19 convalescent plasma include pregnant women.

Considerations in Children

Clinical trials of COVID-19 convalescent plasma in children are ongoing.

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Immunoglobulins: SARS-CoV-2 Specific

Last Updated: July 17, 2020

Recommendation

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

Rationale

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

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

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

Clinical Data

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

Considerations in Pregnancy

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

Considerations in Children

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

Immunoglobulins: Non-SARS-CoV-2 Specific

Last Updated: July 17, 2020

Recommendation

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

Rationale for Recommendation

Currently, only a small proportion of the U.S. population has been infected with SARS-CoV-2. Therefore, it is unknown whether products derived from the plasma of donors without confirmed SARS-CoV-2 infection contain high titer of SARS-CoV-2 neutralizing antibodies. Furthermore, although other blood components in IVIG may have general immunomodulatory effects, it is unclear whether these theoretical effects will benefit patients with COVID-19.

Clinical Data for COVID-19

This study has not been peer reviewed.

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

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

Considerations in Pregnancy

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

Considerations in Children

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

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Mesenchymal Stem Cells

Last Updated: July 17, 2020

Recommendation

- The COVID-19 Treatment Guidelines Panel **recommends against** the use of **mesenchymal stem cells (MSCs)** for the treatment of COVID-19, except in a clinical trial **(AII)**.

Rationale for Recommendation

MSCs are investigational products that have been studied extensively for broad clinical applications in regenerative medicine[1] and for their immunomodulatory properties.[2] No MSCs are approved by the Food and Drug Administration (FDA) for the treatment of COVID-19. There are insufficient data to assess use of MSCs for the treatment of COVID-19.

The FDA has recently issued several warnings about patients being potentially vulnerable to stem cell treatments that are illegal and potentially harmful.[3] Several cord blood-derived products are currently licensed by the FDA for indications such as the treatment of cancer (e.g., stem cell transplant) or rare genetic diseases, and as scaffolding for cartilage defects and wound beds. None of these products are approved for the treatment of COVID-19 or any other viral disease.[4] In the United States, MSCs **should not be used** for the treatment of COVID-19 outside of an FDA-approved clinical trial, expanded access programs, or an Emergency Investigational New Drug application **(AII)**.

Rationale for Use in COVID-19

MSCs are multipotent adult stem cells that are present in most human tissues, including the umbilical cord. MSCs can self-renew by dividing and can differentiate into multiple types of tissues, including osteoblasts, chondroblasts, adipocytes, hepatocytes, and others, which has led to a robust clinical research agenda in regenerative medicine. It is hypothesized that MSCs could reduce the acute lung injury and inhibit the cell-mediated inflammatory response induced by severe acute respiratory syndrome coronavirus 2 (SARS-COV-2). Furthermore, MSCs lack the angiotensin-converting enzyme 2 receptor that SARS-COV-2 uses for viral entry into cells; therefore, MSCs are resistant to infection.[5,6]

Clinical Data

Data supporting the use of MSCs in patients with viral infections, including COVID-19, are limited to case reports and small, open-label studies.

Clinical Data for COVID-19

- A pilot study of intravenous MSC transplantation in China enrolled 10 patients with confirmed COVID-19 categorized according to the National Health Commission of China criteria as critical, severe, or common type. Seven patients (one with critical illness, four with severe illness, and two with common-type illness) received MSCs; three patients with severe illness received placebo. All seven patients who received MSCs recovered. Among the three severely ill control patients, one died, one developed acute respiratory distress syndrome (ARDS), and one remained stable with severe disease.[7]

Clinical Data for Other Viral Infections

- In an open-label study of MSCs for the treatment of H7N9 influenza in China, 17 patients received MSC treatment plus standard of care, and 44 patients received standard of care only. In the MSC

group, three patients (17.6%) died; in the control group, 24 patients (54.5%) died. The 5-year follow-up was limited to five patients in the MSC group. No safety concerns were identified.[8]

Clinical Trials

See *ClinicalTrials.gov* for a list of clinical trials evaluating MSCs for the treatment of COVID-19 and COVID-19-related ARDS that are underway and recruiting participants.

Adverse Effects

Risks associated with MSC transfusion appear to be uncommon. The potential risks include failure of the cells to work as expected, potential for MSCs to multiply or change into inappropriate cell types, product contamination, growth of tumors, infections, thrombus formation, and administration site reactions.[9]

Considerations in Pregnancy

There are insufficient data to assess the risk of MSC use during pregnancy.

Considerations in Children

There are insufficient data on the efficacy and safety of MSC use in children.

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Immunomodulators Under Evaluation for the Treatment of COVID-19

Last Updated: July 17, 2020

Summary Recommendations
Dexamethasone • The COVID-19 Treatment Guidelines Panel (the Panel) recommends using **dexamethasone** (at a dose of 6 mg per day for up to 10 days) for the treatment of COVID-19 in patients who are mechanically ventilated **(AI)** and in patients who require supplemental oxygen but who are not mechanically ventilated **(BI)**. • The Panel **recommends against** using **dexamethasone** for the treatment of COVID-19 in patients who do not require supplemental oxygen **(AI)**. **Other Immunomodulators** There are insufficient data for the Panel to recommend either for or against the use of the following immunomodulators for the treatment of COVID-19: • **Interleukin-1 inhibitors** (e.g., **anakinra**) • **Interleukin-6 inhibitors** (e.g., **sarilumab**, **siltuximab**, **tocilizumab**) • **Interferon-beta** for the treatment of early (i.e., <7 days from symptom onset) mild and moderate COVID-19. The Panel **recommends against** the use of the following immunomodulators for the treatment of COVID-19, except in a clinical trial: • **Interferons (alfa or beta)** for the treatment of severely or critically ill patients with COVID-19 **(AIII)** • **Bruton's tyrosine kinase inhibitors** (e.g., **acalabrutinib**, **ibrutinib**, **zanubrutinib**) and **Janus kinase inhibitors** (e.g., **baricitinib**, **ruxolitinib**, **tofacitinib**) **(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

Corticosteroids (Including Dexamethasone)

Last Updated: July 17, 2020

Recommendation for Patients with COVID-19

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

Rationale

A preliminary, unpublished analysis from a multicenter, randomized, open-label trial (Randomised Evaluation of COVID-19 Therapy [RECOVERY]) in hospitalized patients with COVID-19 showed that patients who were randomized to receive dexamethasone had a lower mortality rate than those who received standard of care. This benefit was observed in patients who required supplemental oxygen at enrollment. No benefit of dexamethasone was seen in patients who did not require supplemental oxygen at enrollment. Details of this trial based on the non-peer-reviewed data in the preliminary analysis are discussed in the Clinical Data to Date section below.[1]

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

Patients with severe COVID-19 can develop a systemic inflammatory response that can lead to lung injury and multisystem organ dysfunction. It has been proposed that the potent anti-inflammatory effects of corticosteroids might prevent or mitigate these deleterious effects. Both beneficial and deleterious clinical outcomes have been reported when corticosteroid (mostly prednisone or methylprednisolone) was used in other pulmonary infectious diseases. In patients with *Pneumocystis jirovecii* pneumonia and hypoxia, prednisone therapy led to decreased mortality;[2] in outbreaks of other novel coronavirus infections (i.e., Middle East respiratory syndrome [MERS] and severe acute respiratory syndrome [SARS]), corticosteroid therapy was associated with delayed virus clearance.[3,4] In severe pneumonia caused by influenza, corticosteroid therapy appears to worsen clinical outcomes, including secondary bacterial infection and mortality.[5]

Corticosteroids have been studied in critically ill patients with acute respiratory distress syndrome (ARDS) with conflicting results.[6-8] Seven randomized controlled trials that included 851 patients evaluated corticosteroids in ARDS.[7-13] However, when the trial results were combined by meta-analysis, corticosteroid therapy was associated with a reduction in both mortality (risk ratio 0.75; 95% confidence interval [CI], 0.59–0.95) and duration of mechanical ventilation (mean difference, -4.93 days, 95% CI, -7.81 to -2.06 days).[14,15]

Monitoring, Adverse Effects, and Drug-Drug Interactions

- Clinicians should closely monitor patients with COVID-19 who are receiving dexamethasone for adverse effects (e.g., hyperglycemia, secondary infections, psychiatric effects).
- Prolonged use of 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. As such, it 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.

- Coadministration of remdesivir and dexamethasone has not been formally studied, but a clinically significant pharmacokinetic interaction is not predicted.

Additional Considerations

- It is not known whether other corticosteroids (e.g., prednisone, methylprednisolone, or hydrocortisone) have a similar benefit as dexamethasone. The total daily dose equivalencies for dexamethasone 6 mg are prednisone 40 mg, methylprednisolone 32 mg, and hydrocortisone 160 mg. Dexamethasone, a long-acting glucocorticoid with a half-life of 36 to 72 hours, is administered once daily; prednisone and methylprednisolone, both intermediate-acting agents with half-lives between 12 and 36 hours, can be administered once daily or in two divided doses daily; hydrocortisone, a short-acting glucocorticoid with a half-life of 8 to 12 hours, is generally administered in two to four divided doses daily.
- Hydrocortisone is commonly used for septic shock in patients with COVID-19; please refer to the Critical Care section for more information.
- Unlike other corticosteroids previously studied in ARDS, dexamethasone lacks mineralocorticoid activity.[10]

Considerations in Pregnancy

A short course of betamethasone and dexamethasone, which are known to cross the placenta, is routinely used to hasten fetal lung maturity and decrease the risk of neonatal respiratory distress syndrome in the premature infant with threatened delivery.[16,17]

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

Considerations in Children

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

Clinical Data to Date

Multicenter, Randomized Controlled Trial of Dexamethasone Versus Standard of Care in Hospitalized Patients

This study has not been peer reviewed.

Study Design

The RECOVERY study is a multicenter, open-label trial sponsored by the National Health Service in the United Kingdom. Eligible participants 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). The primary study endpoint was all-cause mortality at 28 days. Secondary endpoints included time to hospital discharge, cause-specific mortality, need for renal replacement, major cardiac arrhythmia, and receipt/duration of ventilation.[1]

Study Population

Hospitalized patients in the United Kingdom with clinically suspected COVID-19 or laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection were eligible for enrollment. Patients were not enrolled into the dexamethasone study arm (or included in the analysis) if their physicians determined that the risks were too great based on their medical history or that corticosteroid therapy was definitely indicated. Recruitment was stopped by the study steering committee on June 8, 2020, when a sufficient number of participants were enrolled to assess benefit.

Preliminary Results

Participant Characteristics:

- The preliminary analysis included 6,425 participants, with 2,104 participants in the dexamethasone arm and 4,321 in the control arm.
- SARS-CoV-2 infection was confirmed by laboratory testing in 82% of the participants; confirmation of suspected infections was pending at the time of the analysis.
- The mean age of the participants was 66.1 years, 64% of participants were male, and 56% had at least one major comorbidity, including 24% with diabetes.
- At enrollment, 16% of participants required invasive mechanical ventilation, 60% had received supplemental oxygen but no invasive ventilation, and 24% required no oxygen supplementation.
- Few participants received remdesivir, hydroxychloroquine, lopinavir/ritonavir, or tocilizumab (0% to 2% of participants in either arm); approximately 7% of participants in the standard of care arm received dexamethasone after randomization. Use of azithromycin was balanced in both arms (23% vs. 24%).

Study Endpoint Analyses:

- 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% CI, 0.74–0.92, $P < 0.001$).
- There was a statistically significant interaction between baseline severity of COVID-19 and the treatment effect of dexamethasone.
  - Survival benefit was greatest among participants who required invasive mechanical ventilation at randomization: 29.0% of dexamethasone participants died within 28 days of enrollment compared with 40.7% in the control arm (RR 0.65; 95% CI, 0.51–0.82, $P < 0.001$).
  - Among patients who required supplemental oxygen but not mechanical ventilation at enrollment, 21.5% of dexamethasone participants died within 28 days of enrollment compared with 25.0% in the control arm (RR 0.80; 95% CI, 0.70–0.92, $P = 0.002$).
  - No survival benefit was seen among participants who did not require oxygen therapy at enrollment; 17.0% of dexamethasone participants died within 28 days of enrollment compared

to 13.4% in the control arm (RR 1.22; 95% CI, 0.93–1.61, $P = 0.14$).

- Secondary endpoints (e.g., cause-specific mortality, need for renal replacement, major cardiac arrhythmia) have not yet been reported.

Limitations

- The results of the RECOVERY trial have not yet been published in a peer-reviewed journal; full analysis of this study is ongoing.
- The study was randomized, but open label.
- At this time, the results of key secondary endpoints, potential adverse events, and efficacy of dexamethasone in key subgroups (e.g., age groups, patients with comorbidities) have not yet been reported.
- Study participants with COVID-19 who, according to their providers, required oxygen but not mechanical ventilation were a heterogeneous group of patients with respect to their severity of illness; it is unclear whether dexamethasone will be beneficial for other participant subsets (e.g., those who require lower versus higher levels of supplemental oxygen). There were also no standardized or objective criteria for oxygen supplementation.
- The age distribution of participants differed by respiratory status at 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.
- 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.

Interpretation

In patients with severe COVID-19 who required oxygen support, the use of dexamethasone 6 mg daily for up to 10 days reduced mortality at 28 days in a preliminary analysis. The benefit of dexamethasone was most apparent in hospitalized patients who were mechanically ventilated. There was no observed benefit of dexamethasone in those not requiring oxygen support. Further clarity on the mortality benefit of dexamethasone by baseline levels of oxygenation, age, sex, comorbidities, and/or duration of symptoms would better inform application of these findings. More details regarding safety of dexamethasone and longer follow-up would assist in interpretation of this study.

Other Clinical Studies of Corticosteroids in COVID-19

Smaller retrospective cohort and case series studies have yielded conflicting results on the efficacy of corticosteroids for the treatment of COVID-19. Several of these studies demonstrated clinical benefit with the early use of low-dose methylprednisolone, including a more rapid resolution of hypoxia, reduction in requirement for mechanical ventilation, and a reduction in transfer to the intensive care unit and in-hospital length of stay. Additionally, a few of these studies[18] and a small randomized trial revealed a benefit in overall mortality in patients with moderate disease, severe disease, and ARDS,[19,20] consistent with results from the RECOVERY study.

Conversely, several publications from China, including a meta-analysis of 15 studies (which included studies for treatment of COVID-19, SARS, or MERS)[21] and a retrospective review of critically ill patients with COVID-19, suggest an increased risk of multi-organ dysfunction and no benefit in (and

potentially an increased risk of) mortality with use of corticosteroids.[22]

These studies should be interpreted with caution as they are retrospective in nature and have methodological problems.

Clinical Trials

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

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Interferons (Alfa, Beta)

Last Updated: July 17, 2020

Recommendation

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

Rationale

Studies have shown that there was no benefit when interferons were used in patients with other coronavirus infections (i.e., Middle East respiratory syndrome [MERS], severe acute respiratory syndrome [SARS]) with severe or critical disease, and the significant toxicities of interferons outweigh the potential for benefit. Interferons may have antiviral activity early in the course of the infection.

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

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

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

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

Interferon Alfa-2b Treatment for COVID-19

This study has not been peer reviewed.

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

Clinical Data for SARS and MERS

Interferon-beta used alone and in combination with ribavirin in patients with SARS and MERS has failed to show a significant positive effect on clinical outcomes.[4-8]

In a retrospective observational analysis of 350 critically ill patients with MERS[5] from 14 hospitals in Saudi Arabia, mortality was higher among patients who received ribavirin and interferon (beta-1a, alfa-2a, or alfa-2b) than among those who did not receive either drug.

A randomized clinical trial that included 301 patients with acute respiratory distress syndrome[9] found that intravenous interferon beta-1a had no benefit over placebo as measured by ventilator-free days over a 28-day period (median of 10.0 days vs. 8.5 days, respectively) or mortality (26.4% vs. 23.0%, respectively).

Clinical Trials

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

Adverse Effects

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

Drug-Drug Interactions

The most serious drug-drug 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.

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Interleukin-1 Inhibitors

Last Updated: July 17, 2020

Recommendation

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

Rationale

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

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

Rationale for Use in Patients with COVID-19

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

Clinical Data for COVID-19

- A case-control study compared outcomes in 52 consecutive patients with COVID-19 treated with anakinra and 44 historical controls. The patients in both groups were all admitted to the same hospital in Paris, France. Case patients were consecutive admissions from March 24 to April 6, 2020, with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or lung infiltrates on chest imaging typical of COVID-19, and either significant hypoxia (SpO_2 ≤93% with ≥6L/min O_2) or worsening hypoxia (SpO_2 ≤93% with >3L/min O_2 and a loss of ≥3% of O_2 saturation on room air in the previous 24 hours). The historic controls were patients who fulfilled the same eligibility criteria and admitted to the hospital during the same period. As standard of care for both groups, some patients received hydroxychloroquine, azithromycin, or parenteral beta-lactam antibiotics. Anakinra was dosed as 100 mg subcutaneous (SQ) twice daily for 72 hours, followed by anakinra 100 mg SQ daily for 7 days. Clinical characteristics were similar between the groups, except that the cases had a lower mean body mass index than the controls (25.5 kg/m2 vs. 29.0 kg/m^2, respectively), longer duration of symptoms (mean of 8.4 days for cases vs. 6.2 days for controls), and a higher frequency of hydroxychloroquine use (90% for cases vs. 61% for controls) and azithromycin use (49% for cases vs. 34% for controls). The primary outcome of admission to the intensive care unit for mechanical ventilation or death occurred among 13 case patients (25%) and 32 control patients (73%) (hazard ratio 0.22; 95% confidence interval, 0.11 to 0.41). However, within the first 2 days of follow up, in the control group, six patients (14%) had died and 19 patients (43%) had reached the composite primary outcome, which further limited intragroup comparisons and specifically analyses of time to event. C-reactive protein (CRP) levels decreased by Day 4 among those receiving anakinra. Thromboembolic events occurred in 10 patients (19%) who received anakinra and in five control patients (11%). The clinical implications of these findings are uncertain due to limitations in the

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

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

Clinical Trials

See *ClinicalTrials.gov* for a list of clinical trials evaluating anakinra for the treatment of COVID-19.

Adverse Effects

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

Considerations in Pregnancy

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

Considerations in Children

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

Drug Availability

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

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Interleukin-6 Inhibitors

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

Last Updated: July 17, 2020

Recommendation

The COVID-19 Treatment Guidelines Panel **recommends against** the use of **Bruton's tyrosine kinase (BTK) inhibitors**, such as **acalabrutinib**, **ibrutinib**, and **zanubrutinib**; and **Janus kinase (JAK) inhibitors**, such as **baricitinib**, **ruxolitinib**, and **tofacitinib**; for the treatment of COVID-19, except in a clinical trial **(AIII)**.

Rationale

BTK inhibitors and JAK inhibitors have broad immunosuppressive effects. Ongoing clinical trials should help clarify their role in the treatment of COVID-19.

BTK inhibitors are licensed by the Food and Drug Administration (FDA) for the treatment of B-cell malignancies.[1] BTK is a signaling molecule of the B-cell antigen receptor and cytokine receptor pathways. BTK's role in signaling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis, and adhesion.[2]

JAK inhibitors are potent immunosuppressive agents that are FDA approved for the treatment of rheumatoid arthritis, psoriatic arthritis, polycythemia vera, myelofibrosis, ulcerative colitis, and graft-versus-host disease. JAK inhibitors interfere with phosphorylation of signal transducer and activator of transcription (STAT) proteins[3,4] that are involved in vital cellular functions, including signaling, growth, and survival. Phosphorylation of STAT proteins involved in these pathways can increase or decrease their function, and aberrant activation of these proteins has been associated with autoimmune disorders and cancers.[5] JAKs transmit cytokine signaling by pairing with another JAK (e.g., JAK1/JAK2, JAK1/JAK3); however, whether inhibition of specific JAKs is relevant to therapeutic effectiveness is unknown.

Rationale for Use in Patients With COVID-19

The kinase inhibitors are proposed as treatments for COVID-19 because they can prevent phosphorylation of key proteins involved in the signal transduction that leads to immune activation and inflammation (e.g., the cellular response to proinflammatory cytokines such as interleukin [IL]-6).[6] This immunosuppression could potentially reduce the inflammation and associated immunopathologies that have been observed in patients with COVID-19. Additionally, JAK inhibitors, particularly baricitinib, have theoretical direct antiviral activity through interference with viral endocytosis, potentially preventing entry into and infection of susceptible cells.[7]

Adverse Effects

Most of the data on adverse effects of BTK and JAK inhibitors refer to chronic use of the agents. Adverse effects include infections (typically respiratory and urinary tract infections) and the reactivation of herpes viruses. Additional toxicities include myelosuppression and transaminase elevations. Hemorrhage and cardiac arrhythmia have occurred in patients who received BTK inhibitors. Thrombotic events and gastrointestinal perforation have occurred in patients who received JAK inhibitors.

Considerations in Pregnancy

- BTK inhibitors: There is a paucity of data on human pregnancy and BTK inhibitor use. In

animal studies, in doses exceeding the therapeutic human dose, acalabrutinib and ibrutinib were associated with interference with embryofetal development.[8,9] Based on these data, BTK inhibitors may be associated with fetal malformations when use occurs during organogenesis. The impact of use later in pregnancy is unknown. Risks of use should be balanced against potential benefits.

- JAK inhibitors: There is a paucity of data on the use of JAK inhibitors in pregnancy. Fetal risk cannot be ruled out. Pregnancy registries provide some outcome data on tofacitinib used during pregnancy for other conditions (e.g., ulcerative colitis, rheumatoid arthritis, psoriasis). Among the 33 cases reported, pregnancy outcomes were similar to those among the general pregnant population.[10-12] Risks of use should be balanced against potential benefits.

Bruton's Tyrosine Kinase Inhibitors

Acalabrutinib

Acalabrutinib is a second-generation, oral BTK inhibitor that is FDA approved to treat B-cell malignancies (i.e., chronic lymphocytic leukemia/small lymphocytic lymphoma, mantle cell lymphoma). It has a better toxicity profile than first-generation BTK inhibitors (e.g., ibrutinib) due to less off-target activity for other kinases.[13] Acalabrutinib is proposed for use in patients with COVID-19 because it can modulate signaling that promotes inflammation.

Clinical Data for COVID-19

Data regarding acalabrutinib are limited to a retrospective case series of 19 patients with severe COVID-19.[14] However, data interpretation to discern any clinical benefit is limited by the study's small sample size and lack of a control group.

Clinical Trials

Please check *ClinicalTrials.gov* for the latest information on studies of acalabrutinib and COVID-19.

Ibrutinib

Ibrutinib is a first-generation BTK inhibitor that is FDA approved to treat various B-cell malignancies[9] and prevent chronic graft-versus-host disease in stem cell transplant recipients.[15] Based on results from a small case series, ibrutinib has been theorized to improve inflammation and protect against ensuing lung injury in patients with COVID-19.[16]

Clinical Data for COVID-19

Data regarding ibrutinib are limited to an uncontrolled, retrospective case series of six patients with COVID-19 who were receiving ibrutinib for a condition other than COVID-19.[16] However, evaluation of the data for any clinical benefit is limited by the series's small sample size and lack of a control group.

Clinical Trials

Please check *ClinicalTrials.gov* for the latest information on studies of ibrutinib and COVID-19.

Zanubrutinib

Zanubrutinib is a second-generation, oral BTK inhibitor that is FDA approved to treat mantle cell lymphoma.[17] It has been shown to have fewer toxicities than first-generation BTK inhibitors (e.g., ibrutinib) due to less off-target activity for other kinases.[18] Zanubrutinib is proposed to be of use in patients with COVID-19 by modulating signaling that promotes inflammation.

Clinical Data for COVID-19

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

Clinical Trials

Please check *ClinicalTrials.gov* for the latest information on studies of zanubrutinib and COVID-19.

Janus Kinase Inhibitors

Baricitinib

Baricitinib is an oral JAK inhibitor that is selective for JAK1 and JAK2 and FDA approved for the treatment of rheumatoid arthritis.[19] Among the JAK inhibitors studied, baricitinib has been postulated to have the greatest theoretical antiviral efficacy in inhibiting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from entering and infecting lung cells because of its affinity for adaptor-associated kinase-1 (AAK1), a regulator of viral endocytosis in pulmonary alveolar type 2 (AT2) epithelial cells.[20] In addition, baricitinib can modulate downstream inflammatory responses via inhibition of JAK1/JAK2 kinase and has exhibited dose-dependent inhibition of IL-6-induced STAT3 phosphorylation.[21]

Clinical Data for COVID-19

This study has not been peer-reviewed.

A small, nonrandomized study in patients with moderate COVID-19 pneumonia compared combination therapy with baricitinib and lopinavir/ritonavir to standard of care (SOC) therapy (i.e., combination lopinavir/ritonavir and hydroxychloroquine). Both study groups included 12 patients. Compared to SOC therapy, combination therapy with baricitinib and lopinavir/ritonavir demonstrated a statistically significant shorter time to improvement of clinical and respiratory symptoms and a greater reduction of C-reactive protein levels.[22]

Clinical Trials

Please check *ClinicalTrials.gov* for the latest information on studies of baricitinib and COVID-19.

Ruxolitinib

Ruxolitinib is an oral JAK inhibitor selective for JAK1 and JAK2 and is currently approved for myelofibrosis, polycythemia vera, and acute graft-versus-host disease.[23] Like baricitinib, it is theorized to have antiviral properties through inhibition of AAK1, which may prevent viral entry and infection of pulmonary AT2 epithelial cells.[7]

Clinical Data for COVID-19

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

among the patients who had detectable viral loads at the time of randomization to ruxolitinib treatment (n = 8) or placebo (n = 9). Limitations of this study include the small sample size, the exclusion of ventilated patients at study entry, and the frequent concomitant use (among 70% of patients) of antivirals and steroids.[24]

A small, retrospective, single-arm study in Germany reported no safety concerns in 14 patients with severe COVID-19 who received a brief course of ruxolitinib therapy (with a median of 9 days of treatment).[25]

Clinical Trials

Please check *ClinicalTrials.gov* for the latest information on studies of ruxolitinib and COVID-19.

Tofacitinib

Tofacitinib is the prototypical JAK inhibitor, predominantly selective for JAK1 and JAK3, with modest activity against JAK2, and, as such, can block signaling from gamma-chain cytokines (e.g., IL-2, IL-4) and gp 130 proteins (e.g., IL-6, IL-11, interferons). It is an oral agent first approved for the treatment of rheumatoid arthritis and has been shown to decrease levels of IL-6 in patients with this disease.[26] Tofacitinib is also FDA approved for the treatment of psoriatic arthritis and ulcerative colitis.[27]

Clinical Data for COVID-19

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

Clinical Trials

Please check *ClinicalTrials.gov* for the latest information on studies of tofacitinib and COVID-19.

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

Last Updated: July 17, 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-Derived Products			
COVID-19 Convalescent Plasma	• The FDA has provided recommendations for the use of COVID-19 convalescent plasma through EINDs for individual patients, traditional INDs, or expanded access INDs. 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 on that specific program and other trials evaluating convalescent plasma.	• Plasma donated from individuals who have recovered from COVID-19 includes antibodies to SARS-CoV-2.[1] Thousands of U.S. patients have received convalescent plasma through clinical trials, expanded access treatment trials, and EIND applications. However, the standards and methods for screening donated plasma for SARS-CoV-2 binding and neutralizing antibodies have not been established. The variability in SARS-CoV-2 antibody levels in donor plasma may impact the product's efficacy. Clinical data are currently insufficient to evaluate the efficacy of convalescent plasma.	**For COVID-19:** • *Open-Label, Randomized Clinical Trial of Convalescent Plasma in 103 Hospitalized Patients With Severe or Life-Threatening COVID-19:* Investigators conducted an open-label, randomized clinical trial of convalescent plasma versus SOC for patients with severe and life-threatening laboratory-confirmed COVID-19 in seven medical centers in Wuhan, China, from February 14 to April 1, 2020. The primary outcome was time to clinical improvement within 28 days, which was defined as patient discharged alive or a reduction of 2 points on a 6-point disease severity scale. Only plasma units with SARS-CoV-2 viral spike-receptor binding domain-specific IgG titer ≥ 1:640 were transfused. The median dose of ABO-compatible convalescent plasma was 200 mL. The time from symptom onset to randomization was 27 days in the treatment group and 30 days in the control group. Due to control of the COVID-19 outbreak in Wuhan, the trial was terminated early after 103 of the planned for 200 patients were enrolled. The convalescent plasma and control groups were well balanced by age (median age of 70 years vs. 69 years, respectively), but the control group had a higher proportion of men (65%) than the convalescent plasma group (52%). Baseline severity scores (45 patients had severe disease and 58 had life-threatening disease) and use of concomitant therapies were similar between the two groups. There was no significant difference between the groups in the primary outcome of time to clinical improvement within 28 days (HR 1.40; 95% CI, 0.79–2.49; $P = 0.26$). Among those with severe disease, 91% of the convalescent plasma recipients and 68% of the control patients improved by Day 28 (difference 23%; OR 1.34; 95% CI, 0.98–1.83; $P = 0.07$). Among those with life-threatening disease, 21% of the convalescent plasma recipients and 24% of the control patients improved by Day 28 (difference -3.4%; OR 0.86; 95% CI, 0.33–2.24; $P = 0.75$). There was no significant difference in 28-day mortality between the groups (16% vs. 24% for the treatment and control groups, respectively; OR 0.65; 95% CI, 0.29–1.46; $P = 0.30$). At 24, 48, and 72 hours, the rates of negative SARS-CoV-2 viral PCR were significantly higher in the convalescent plasma group than in the control group (45% vs. 15%, $P = 0.003$ at 24 hours; 68% vs. 33%, $P = 0.001$ at 48 hours; and 87% vs.

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-Derived Products, continued			
COVID-19 Convalescent Plasma, continued			38%, *P* <0.001 at 72 hours). Two transfusion-related events were reported, including 1 severe event; both events resolved with supportive care. The study's primary limitations were its open-label design and that, on average, administration of the convalescent plasma was approximately 1 month into the disease course. In addition, the study was terminated early, and thus the sample size was insufficient to detect differences in clinical outcomes.[2] • *Preliminary Safety Analysis of the First Consecutive 5,000 Patients to Receive Open Label, COVID-19 Convalescent Plasma Through a National Expanded Access Program:*[3] The Expanded Access to Convalescent Plasma for the Treatment of Patients with COVID-19 program is an ongoing, open-label, nonrandomized protocol primarily designed to provide patients with severe or life-threatening (critical) COVID-19 with access to convalescent plasma, which is an investigational product in the United States. Secondary objectives were to obtain safety data on the product. The protocol is sponsored by the Mayo Clinic and includes a diverse range of clinical sites. Plasma donors have documented COVID-19, with complete resolution of symptoms for at least 14 days prior to donation, and are either male, female without history of pregnancy, or female with history of pregnancy and negative HLA testing after the most recent pregnancy. SARS-Cov-2 antibody testing of donors is not mandated. ABO-compatible convalescent plasma is transfused preferentially, but in the absence of ABO-compatible plasma, patients may receive either Group A plasma or low anti-A titer Group O plasma, as available. The main safety outcomes for the safety analysis are SAEs including death; SAEs are reported at 4 hours and at 7 days after transfusion, or as they occur. The safety analysis describes the first 5,000 patients, enrolled between April 7 and May 3, 2020. Participants were adults with median age of 62 years, 63% male, and 81% had severe or life-threatening COVID-19. SAEs were reported in 36 patients (<1%) within 4 hours of transfusion; SAEs included 15 deaths, including 4 possibly or probably related to the convalescent plasma treatment. The 21 non-fatal SAEs included 7 TACO events, 11 TRALI events, and 3 severe allergic reactions. The overall 7-day mortality rate was 14.9%. In this study, COVID-19 convalescent plasma therapy was associated with a low rate (<1%) of serious transfusion-related events. The study design, which does not include a control arm, precludes an assessment of efficacy or ADE. • *Retrospective, Single-Center, Case-Control Study Evaluating Convalescent Plasma Plus Standard of Care Versus Standard of Care Without Convalescent Plasma:*[4] *Not Peer Reviewed.* This case-control study reports clinical outcomes among 39 consecutive patients who received COVID-19 convalescent plasma through the FDA's single patient EIND program while hospitalized at Mount Sinai Hospital in New York City during the

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-Derived Products, continued			
COVID-19 Convalescent Plasma, continued			period March 24 to April 8, 2020. Recipients were transfused with 2 units of ABO-compatible convalescent plasma from donors with a SARS-CoV-2 antispike antibody titer of 1:320 dilution. The control group (n = 156) was identified retrospectively from the hospital's EHR database. The control patients were hospitalized during the same period as the patients in the convalescent plasma group and had confirmed COVID-19 but did not receive convalescent plasma. They were matched 4:1 to the convalescent plasma recipients using propensity scores to correct for measured confounders. Convalescent plasma recipients had a mean age of 55 years and 64% were male. At the time of transfusion, 87% of the recipients required supplemental oxygen (noninvasive) and 10% were mechanically ventilated. By Day 14, the clinical condition had worsened in 18% of the convalescent plasma patients and 24% of the control patients ($P = 0.17$). As of May 1, 2020, 13% of the plasma recipients and 24% of the matched control patients had died ($P = 0.04$, log-rank test) and 72% of the transfused patients and 67% of the control patients had been discharged. Interpretation of the study results is limited by the lack of randomization and the potential for unmeasured patient selection bias. • Other smaller, uncontrolled case series describing clinical outcomes in patients with COVID-19 have been reported and also suggest that serious AEs are uncommon following COVID-10 convalescent plasma treatment.[5-10]
SARS-CoV-2 Specific Immunoglobulins	• Not approved by the FDA	• Concentrated antibody preparations derived from pooled plasma collected from individuals who have recovered from COVID-19 can be manufactured as SARS-CoV-2 immunoglobulin, which could potentially suppress the virus and modify the inflammatory response.	• No clinical data for COVID-19, SARS, or MERS

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-Derived Products, continued			
Non-SARS-CoV-2 Specific Intravenous Immunoglobulins	• Primary immune disorders • Thrombocytopenic purpura • Kawasaki disease • Motor neuropathy • Prophylaxis of various bacterial and viral infections	• 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 without confirmation of SARS-CoV-2 infection are not likely to contain SARS-CoV-2 antibodies. Furthermore, although IVIG contains other blood components that may have general immunomodulatory effects, it is unclear if these theoretical immunomodulatory effects will benefit patients with COVID-19.	**For COVID-19:** • *Not Peer Reviewed.* A retrospective, nonrandomized cohort study of IVIG for the treatment of COVID-19 was conducted across eight treatment centers in China between December 2019 and March 2020. The study found no difference in 28-day or 60-day mortality between 174 patients who were treated with IVIG and 151 patients who were not treated with IVIG. Patients who received IVIG were hospitalized for longer (median stay of 24 days for IVIG group vs. 16 days for no IVIG group) and experienced longer duration of disease (median of 31 days for IVIG group vs. 23 days for no IVIG group). 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 patients [21%] in the non-IVIG group). A subgroup analysis that was limited to the critically 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 or no IVIG, and the patients in the IVIG group were older and more likely to have coronary heart disease than those in the no IVIG group. The IVIG group also had more patients with severe COVID-19 disease at study entry. Also, patients in both groups received many concomitant therapies for COVID-19.[11]
Mesenchymal Stem Cells (MSCs)	• Not approved by the FDA	• Multipotent adult stem cells that are present in most human tissues including the umbilical cord • It is hypothesized that MSCs could reduce the acute lung injury and inhibit the cell-mediated inflammatory response induced by SARS-COV-2. • MSCs lack the angiotensin-converting enzyme 2 receptor that SARS COV-2 uses for viral entry into cells; therefore, MSCs are resistant to infection.[12,13]	**For COVID-19:** • A pilot study of IV MSC transplantation in China enrolled 10 patients with confirmed COVID-19 categorized according to the National Health Commission of China criteria as critical, severe, or common-type disease. Seven patients (1 with critical illness, 4 with severe illness, and 2 with common-type illness) received MSCs; 3 patients with severe illness received placebo. All 7 patients who received MSCs recovered. Among the 3 severely ill control patients, 1 died, 1 developed ARDS, and 1 remained stable with severe disease.[14] **For Other Viruses:** • In an open-label study of MSCs for the treatment of H7N9 influenza in China, 17 patients received MSC treatment plus SOC, and 44 patients received SOC only. In the MSC group, 3 patients (17.6%) died; in the control group, 24 patients (54.5%) died. The 5-year follow-up was limited to 5 patients in the MSC group. No safety concerns were identified.[15]

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)
Immunomodulators			
Corticosteroids			
Dexamethasone	**FDA-Approved Indications:** • Allergic states (e.g., severe or incapacitating asthma, dermatitis, drug HSRs) • Dermatologic diseases (e.g., bullous dermatitis, Stevens-Johnson syndrome) • Endocrine disorders (e.g., adrenocortical insufficiency) • Gastrointestinal diseases (e.g., ulcerative colitis) • Hematologic disorders (e.g., hemolytic anemia, idiopathic thrombocytopenia purpura, pure red cell aplasia) • Neoplastic diseases (e.g., palliative treatment of leukemia, lymphoma) • Nervous system disorders (e.g., multiple sclerosis, cerebral edema) • Ophthalmic diseases (e.g., temporal arteritis, uveitis) • Renal diseases (e.g., to induce diuresis or remission of proteinuria in idiopathic nephrotic syndrome) • Respiratory diseases (e.g., eosinophilic pneumonia) • Rheumatic disorders (e.g., ankylosing spondylitis, rheumatoid arthritis, systemic lupus erythematosus)[16]	• Long-acting potent synthetic glucocorticoid with minimal mineralocorticoid activity. Glucocorticoid activity includes anti-inflammatory, immunosuppressive, anti-proliferative, and vasoconstrictive effects.[17] • Potent anti-inflammatory effects may mitigate or prevent the systemic inflammatory response associated with severe COVID-19.	**For COVID-19:** • A preliminary, unpublished analysis from a large multicenter, randomized, open-label trial (RECOVERY) in hospitalized patients in the United Kingdom showed that those randomized to dexamethasone 6 mg daily (n = 2,104) had reduced mortality within 28 days of enrollment compared with those who received SOC (n = 4,321) (21.6% vs. 24.6%; RR 0.83; 95% CI, 0.74–0.92, $P < 0.001$). The survival benefit was greatest among participants who required invasive mechanical ventilation at randomization: 29.0% of participants in the dexamethasone group died within 28 days of enrollment compared with 40.7% of those in the control arm (RR 0.65; 95% CI, 0.51–0.82, $P < 0.001$). Among patients who required supplemental oxygen but not mechanical ventilation at enrollment, 21.5% in the dexamethasone arm died within 28 days of enrollment compared with 25.0% of those in the control arm (RR 0.80; 95% CI, 0.70–0.92, $P = 0.002$). No survival benefit was seen among participants who did not require oxygen therapy at enrollment; 17.0% of dexamethasone participants died within 28 days of enrollment compared with 13.4% in the control arm (RR 1.22; 95% CI, 0.93–1.61, $P = 0.14$). Interpretation of these results is limited by several factors: full analysis of the trial is ongoing; the results of key secondary endpoints, potential adverse events, and efficacy in key subgroups have not been reported; there were not standardized or objective criteria for oxygen supplementation; and the age distribution of patients differed by respiratory status at the time of randomization (patients who received mechanical ventilation were more likely to be <70 years of age).[18] • Small retrospective cohort studies and case series have yielded conflicting results regarding corticosteroids, with some suggesting benefits associated with short courses of corticosteroids[19-22] and others showing potential harm.[23,24] • Conversely, several publications from China including a meta-analysis of 15 studies (which included studies for treatment of COVID-19, SARS, or MERS)[24] and a retrospective review of critically ill patients with COVID-19 suggest an increased risk of multi-organ dysfunction and no benefit in (to possibly increased risk of) mortality with use of corticosteroids.[25]

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	• 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[26-28]	**For COVID-19:** • An open-label, Phase 2 clinical trial randomized 127 participants (median age 52 years) 2:1 to combination antiviral therapy or LPV/r. In the combination antiviral therapy group, the treatment regimen differed by time from symptom onset to hospital admission. Participants admitted within 7 days of symptom onset (n = 76) were randomized to triple drug therapy (IFN beta-1b 8 million units SQ every other day for up to 7 days total, LPV/r, and ribavirin); those admitted ≥7 days after symptom onset (n = 51) were randomized to double therapy (LPV/r and ribavirin) because of concerns regarding potential inflammatory effects of IFN. All participants in the control group received LPV/r alone regardless of time from symptom onset to hospitalization. The study participants were patients in Hong Kong with confirmed SARS-CoV-2 infection who were hospitalized regardless of disease severity until they had two negative nasopharyngeal swabs. The median time to a negative SARS-CoV-2 PCR on a nasopharyngeal swab (the primary endpoint) was shorter for the combination group than for the control group (7 days vs. 12 days, $P = 0.001$). The combination group had more rapid clinical improvement as assessed by NEWS2 and SOFA score and a shorter hospital stay (9 days for combination group vs. 14.5 days for control group, $P = 0.016$). There was no difference in oxygen use between the groups. The antiviral and clinical effect was more pronounced in the patients hospitalized within 7 days of symptom onset suggesting that IFN beta-1b with or without ribavirin was the critical component of the combination therapy. The study provides no information about the effect of IFN beta-1b administered >7 days after symptom onset.[29] • *Not Peer Reviewed.* In a retrospective cohort study of 77 adults with moderate COVID-19 in China, those who used nebulized IFN alfa-2b with or without umifenovir (Arbidol) achieved viral clearance in the upper respiratory track faster and had lower systemic inflammation than those who used only umifenovir. However, results are difficult to interpret because participants in the IFN alfa-2b group were substantially younger than those in the umifenovir only group (mean age 40 years vs. 65 years) and had fewer comorbidities (15% vs. 54%) at study entry. The nebulized formulation of IFN alfa-2b is not FDA approved for use in the United States.[30]
Interferon Beta	• 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)[26,31] • Among IFN subtypes, IFN beta-1b shows greatest *in vitro* inhibition of MERS-CoV.[32,33] • *In vitro* activity against MERS-CoV in lung cells.[34]	

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			
Anakinra	• Rheumatoid arthritis • Cryopyrin-associated periodic syndromes, specifically neonatal-onset multisystem inflammatory disease[35] • IV formulation is not approved for use in the United States	• Competitively inhibits IL-1 binding to the IL-1 type I receptor	**For COVID-19:** • A case-control study compared outcomes in 52 consecutive patients with COVID-19 treated with anakinra to outcomes in 44 historical controls. The patients in both groups were admitted to the same hospital system in Paris, France. Cases were consecutive admissions from March 24 to April 6, 2020, with laboratory-confirmed SARS-CoV-2 infection or lung infiltrates on chest imaging typical of COVID-19, and either significant hypoxia (SpO_2 ≤93% with ≥6L/min O_2) or worsening hypoxia (SpO_2 ≤93% with >3L/min O_2 and a loss of ≥3% of O_2 saturation on room air in the previous 24 hours). Historic controls were patients fulfilling the same eligibility criteria and admitted to the hospital from March 18 to March 24, 2020. SOC for both groups entailed use of HCQ, AZM, and parenteral beta-lactam antibiotics. Anakinra was dosed SQ as 100 mg twice daily for 72 hours, followed by anakinra 100 mg daily for 7 days. Clinical characteristics were similar between the groups, except that the case patients had a lower mean BMI (25.5 kg/m^2 for cases vs. 29.0 kg/m^2 for controls), longer duration of symptoms (8.4 days for cases vs. 6.2 days for controls), and a higher frequency of HCQ use (90% for cases vs. 61% for controls) and AZM use (49% for cases vs. 34% for controls). The primary outcome of either admission to the ICU for mechanical ventilation or death occurred among 13 cases (25%) and 32 controls (73%) (HR 0.22; 95% CI, 0.11–0.41). However, within the first 2 days of follow up, in the control group, 6 patients (14%) had died and 19 patients (43%) had reached the composite primary outcome, which further limited intragroup comparisons and specifically analyses of time to event. CRP levels decreased by Day 4 among those receiving anakinra. Thromboembolic events occurred in 10 patients (19%) in the anakinra group and 5 patients (11%) in the control group. The clinical implications of these findings are uncertain, due to limitations in the study design related to unmeasured confounding combined with the very high early event rate among the retrospective controls.[36] • A single-center case series reported on open-label use of anakinra in 9 hospitalized patients with COVID-19, presenting with 4–12 days of symptoms, requiring oxygen ≤6 L/min, 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 patients also received HCQ plus AZM; the other 7 patients received no specific additional treatments. Anakinra was discontinued in one patient who progressed to acute respiratory failure after the first dose 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-1 Inhibitor, continued			
Anakinra			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 had 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.[37] • A single-center, retrospective, cohort study in Italy compared outcomes in 29 patients following open-label anakinra use with outcomes in 16 historical controls. All patients had COVID-19 with moderate to severe ARDS requiring noninvasive ventilation, and evidence of hyperinflammation. High-dose IV anakinra 5 mg/kg twice daily 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 rate 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 age of 62 years in anakinra group vs. 70 years in control group), and fewer patients had chronic kidney disease. High-dose anakinra was discontinued in 7 patients (24%) due to AEs (bacteremia in 4 patients, elevated liver enzymes in 3 patients); however, retrospective assessment showed that these events occurred with similar frequency in the control group. An additional group of 7 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.[38]
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[39]	• Human recombinant monoclonal antibody • IL-6 receptor antagonist[40]	**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 critically 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

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			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%). 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 patients with critical illness, the press release cited "negative trends" for most outcomes in patients with severe illness who received sarilumab.[41]
Siltuximab	• Multicentric Castleman disease	• Human-mouse chimeric monoclonal antibody • IL-6 antagonist[42]	**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 (7 of 21 patients) following siltuximab treatment. Other patients experienced no clinically relevant change in condition (9 of 21 patients) or worsening condition (5 of 21 patients). Among the 5 patients with worsening condition, there was 1 death and 1 cerebrovascular event (median follow-up of 8 days).[43]
Tocilizumab	• Cytokine release syndrome (induced by CAR T-cell therapy) • Rheumatoid arthritis • Giant cell arteritis • Polyarticular juvenile idiopathic arthritis • Systemic juvenile idiopathic arthritis[44]	• 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 7 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.

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			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% (7 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 tocilizumab, but provide no details regarding a comparison group or specify an a-priori comparison, which limits interpretation of this result.[45] • An uncontrolled, retrospective cohort study of 21 hospitalized COVID-19 patients who received tocilizumab reported improvement in oxygenation and systemic inflammation. At study entry, among the 21 patients (mean age 56 years; range 25 to 88 years), 17 had severe disease and 4 had critical disease. All patients were febrile, had abnormal chest CT findings, and required oxygen supplementation (2 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 g/mL, and mean lymphocyte percentage was 15.5%. Eighteen patients were given tocilizumab IV infusion once, and within 12 hours, 3 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.[46] • Additional data supporting the use of tocilizumab for COVID-19 include a small retrospective cohort study, a case series, and a case-control study.[47-49]

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*)
Kinase Inhibitors: Bruton's Tyrosine Kinase Inhibitors			
Acalabrutinib	• Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) • Mantle cell lymphoma (MCL)[50]	• Second-generation oral BTK inhibitor • Inhibits BTK signaling of the B-cell antigen receptor and cytokine receptor pathways • Potential modulation of signaling that promotes inflammation and cytokine storm[51]	**For COVID-19:** • Data regarding acalabrutinib are limited to a retrospective case series in 19 patients with severe COVID-19. However, data interpretation to discern any clinical benefit is limited by the study's small sample size and lack of a control group.[52]
Ibrutinib	• Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) • Mantle cell lymphoma (MCL) • Marginal zone lymphoma (MZL) • Waldenström macroglobulinemia (WM) • Chronic graft-versus-host disease (cGVHD) in stem cell transplant recipients[53]	• First-generation oral BTK inhibitor • Inhibits BTK signaling of the B-cell antigen receptor and cytokine receptor pathways • Potential modulation of signaling that promotes inflammation and cytokine storm[54]	**For COVID-19:** • Data regarding ibrutinib are limited to an uncontrolled, retrospective case series of 6 patient with COVID-19 who were receiving ibrutinib for a condition other than COVID-19. However, evaluation of the data for any clinical benefit is limited by the study's small sample size and lack of control group.[54]
Zanubrutinib	• Mantle cell lymphoma (MCL)[55]	• Second-generation oral BTK inhibitor • Inhibits BTK signaling of the B-cell antigen receptor and cytokine receptor pathways • Potential modulation of signaling that promotes inflammation and cytokine storm[51]	• No clinical data for COVID-19, SARS, or MERS

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)
Kinase Inhibitors: Janus Kinase Inhibitors			
Baricitinib	• Rheumatoid arthritis[56]	• JAK inhibitor selective for JAK1, JAK2, and TYK2, relative to JAK3 • Theoretical direct antiviral activity through inhibition of kinases (AAK1 and cyclin G-associated kinase) that regulate viral endocytosis in pulmonary AT2 epithelial cells, which may prevent SARS-CoV-2 entry into and infection of susceptible cells. • Dose-dependent inhibition of IL-6 induced STAT3 phosphorylation[57]	**For COVID-19:** • *Not Peer Reviewed.* A small, nonrandomized study of 12 patients with moderate COVID-19 pneumonia compared therapy with baricitinib and LPV/r with SOC alone (i.e., combination LPV/r and HCQ).[58] Baricitinib and LPV/r therapy demonstrated a statistically significant time to improvement in clinical and respiratory symptoms and reduction in measured CRP.[58]
Ruxolitinib	• Myelofibrosis • Polycythemia vera • Steroid-refractory acute graft-versus-host disease[59]	• JAK inhibitor selective for JAK1 and JAK2 • Theoretical antiviral properties through inhibition of AAK1 which may prevent viral entry into and infection of pulmonary AT2 alveolar epithelial cells[60,61] • Inhibition of IL-6 via JAK1/JAK2 pathway inhibition	**For COVID-19:** • A small, prospective, single-blind randomized controlled Phase 2 trial in patients with COVID-19 in China compared ruxolitinib 5 mg PO twice daily (n = 20) to placebo (vitamin C 100 mg; n = 21), both given in combination with SOC therapy. The median age of the patients was 63 years. There were no significant demographic differences between the two arms. Treatment with ruxolitinib was associated with a non-significant reduction in median time to clinical improvement (12 days for ruxolitinib vs. 15 days for placebo; $P = 0.15$), defined as a 2-point improvement on a 7-category ordinal scale or hospital discharge. There was no difference between the groups in the median time to discharge (17 days for ruxolitinib vs. 16 days for placebo; $P = 0.94$). More patients in the ruxolitinib group than in the placebo group had radiographic improvement on CT scans of the chest at Day 14 (90% for ruxolitinib vs. 61.9% for placebo; $P = 0.05$), and a shorter time to recovery from initial lymphopenia when present (5 days for ruxolitinib vs. 8 days for placebo; $P = 0.03$). The use of ruxolitinib was not associated with an increased risk of AEs or mortality (no deaths in the ruxolitinib group vs. 3 deaths [14% of patients] in the control group). Despite the theoretical antiviral properties of JAK inhibitors, there was no significant difference in time to viral clearance among patients who had detectable viral loads at randomization to ruxolitinib (n = 8) or placebo (n = 9). Limitations of this study include the small sample size, the exclusion of ventilated patients at study entry, and the frequent concomitant use (by 70% of patients) of antivirals and steroids.[62] • A small retrospective single-arm study in Germany reported no safety concerns in 14 patients with severe COVID-19 who received a brief course of ruxolitinib therapy (median 9 days).[63]

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*)
Kinase Inhibitors: Janus Kinase Inhibitors, continued			
Tofacitinib	• Rheumatoid arthritis • Psoriatic arthritis • Ulcerative colitis[64]	• JAK inhibitor selective for JAK1 and JAK3 with modest activity against JAK2 • Blocks signaling from gamma-chain cytokines (IL-2, IL-4) and gp 130 proteins (IL-6, IL-11, IFNs) • Shown to decrease levels of IL-6 in rheumatoid arthritis[65]	• No clinical data for COVID-19, SARS, or MERS

Key: AAK1 = Adaptor-associated kinase 1; ADE = antibody-dependent enhancement; AE = adverse event; ARDS = acute respiratory distress syndrome; ARV = antiretroviral; AT2 = alveolar type 2; AZM = azithromycin; BTK = Bruton's tyrosine kinase; CAR = chimeric antigen receptor; CRP = C-reactive protein; CI = confidence interval; CT = computerized tomography; EHR = electronic health record; EIND = Emergency Investigational New Drug Application; FDA = Food and Drug Administration; GAK = cyclin G-associated kinase; HCQ = hydroxychloroquine; HR = hazard ratio; HSR = hypersensitivity reaction; ICU = intensive care unit; IDMC = independent data monitoring committee; IFN = interferon; IL = interleukin; IND = Investigational New Drug application; 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; MSC = mesenchymal stem cells; NEWS2 = National Early Warning Score 2; OR = odds ratio; PCR = polymerase chain reaction; PI = protease inhibitor; RR = age-adjusted rate ratio; SARS = severe acute respiratory syndrome; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOC = standard of care; SOFA = sequential organ failure assessment; SQ = subcutaneous; STAT3 = signal transducer and activator of transcription 3; TACO = transfusion-associated circulatory overload, TRALI = transfusion-related acute lung injury

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

Last Updated: July 17, 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 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 associated with immune-based therapy in patients with COVID-19 are not well defined. Whether the frequency and severity of AEs associated with use of these agents for FDA approved-indications is the same in patients with COVID-19, especially in critically ill patients, is unknown. 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	Single or multiple transfusions based on patient response	• TRALI • TACO • Allergic reactions • Antibody-mediated enhancement of infection • Red cell alloimmunization • Transmission of infectious pathogens[1] • Thrombotic events	• Monitor for transfusion-related reactions. • 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 immunoglobulins for the treatment of COVID-19. • A list of clinical trials is available: Convalescent Plasma
Immunoglobulins: SARS-CoV-2 Specific	Varies by clinical trial	• TRALI • TACO • Allergic reactions • Antibody-mediated enhancement of infection • Red cell alloimmunization • Transmission of infectious pathogens	• Monitor for transfusion-related reactions. • 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 for the Panel to recommend either for or against SARS-CoV-2 immunoglobulins for the treatment of COVID-19. • A list of clinical trials is available: 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
Blood Products, continued					
Immunoglobulins: Non-SARS-CoV-2 Specific	Doses vary based on indication and formulation.	• Allergic reactions including anaphylaxis • Renal failure • Thrombotic events • Aseptic meningitis syndrome • Hemolysis • TRALI • Transmission of infectious pathogens	• Monitor for transfusion-related reactions. • 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. • AEs may vary by formulation. • AEs may be precipitated by high dose, rapid infusion, or underlying conditions. • A list of clinical trials is available: Intravenous Immunoglobulin
Mesenchymal Stem Cells	Varies by clinical trial Mesenchymal stem cells should not be used in the United States for the treatment of COVID-19 outside of an FDA-approved clinical trial, expanded access protocol, or EIND process.	• Failure of the cells to work as expected[2] • Potential for mesenchymal stem cells to multiply or change into inappropriate cell types • Product contamination • Growth of tumors • Infections • Thrombus formation[3] • Administration site reactions[4,5]	• Monitor for administration site reactions.	Drug products should not be added to the IV infusion line for the MSC product.	• The Panel **recommends against** the use of mesenchymal stem cells for the treatment of COVID-19, except in a clinical trial **(AII)**. • The FDA has issued several warnings about patients being potentially vulnerable to stem cell treatments that are illegal and potentially harmful.[4] A number of cord blood-derived products are currently licensed by the FDA for various indications such as the treatment of cancer (stem cell transplant) and rare genetic diseases. These products are not FDA approved for the treatment of COVID-19. • A list of clinical trials is available: Mesenchymal Stem Cells

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
Immunomodulators					
Corticosteroids					
Dexamethasone	**For COVID-19:** • Dexamethasone 6 mg daily IV or PO, for up to 10 days[6]	• Hyperglycemia • Secondary infections • Reactivation of latent infections (e.g., HBV, HSV, strongyloidiasis, TB) • Psychiatric disturbances • Adrenal insufficiency • Increased blood pressure • Peripheral edema • Myopathy (particularly if used with neuromuscular blocking agents) • In outbreaks of other novel coronavirus infections (i.e., MERS and SARS), corticosteroid therapy was associated with delayed virus clearance.[7,8]	• Blood glucose • Blood pressure • Sign and symptoms of new infection	• Moderate CYP3A4 inducer • CYP3A4 substrate • Minimal to no reduction in remdesivir exposure is expected with coadministration of dexamethasone (Gilead communication).	• The Panel recommends using dexamethasone (at a dose of 6 mg per day for up to 10 days) for the treatment of COVID-19 in patients who are mechanically ventilated **(AI)** and in patients who require supplemental oxygen but who are not mechanically ventilated **(BI)**. • The Panel **recommends against** using dexamethasone for the treatment of COVID-19 in patients who do not require supplemental oxygen **(AI)**. • Currently, it is not known whether other corticosteroids (e.g., prednisone, methylprednisolone, or hydrocortisone) will provide a benefit like that with use of dexamethasone. The approximate daily doses equivalent to dexamethasone 6 mg daily for prednisone, methylprednisolone, and hydrocortisone are 40 mg, 32 mg, and 160 mg, respectively. • Remdesivir was not part of the treatment in the RECOVERY trial, therefore the safety and efficacy of remdesivir and dexamethasone used together are not known. • Dexamethasone is available as oral tablet, oral solution, oral elixir, and IV solution • A list of clinical trials is available: Dexamethasone

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[9,10] **IFN Alfa-2b:** • *COVID-19 Clinical Trial Dosing:* Nebulized IFN alfa-2b 5 million units twice daily (no duration listed in the study)[11]	• Flu-like symptoms (e.g., fever, fatigue, myalgia)[12] • Injection site reactions • Liver function abnormalities • Decreased blood counts • Worsening depression • Insomnia • Irritability • Nausea • Vomiting • Hypertension • Induction of autoimmunity	• CBC with differential • Liver enzymes; 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 IFNs for the treatment of severely and critically ill COVID-19 patients, except in a clinical trial **(AIII)**. • For COVID-19, IFN-alfa has primarily been used as nebulization and usually as part of a combination regimen. • Nebulized IFN-alfa-2b is not approved in the United States. • IFN alfa-1b is not approved in the United States. • 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

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, continued					
Interferon Beta	**IFN Beta-1a:** • 44 mcg SQ three times weekly[10] for MERS • Duration for COVID-19 unknown **IFN Beta-1b:** • 8 million units SQ, every other day, up to 7 days total for COVID-19[13]	• Flu-like symptoms (e.g., fever, fatigue, myalgia)[14] • Leukopenia, neutropenia, thrombocytopenia, lymphopenia • Liver function abnormalities (ALT > AST) • Injection site reactions • Headache • Hypertonia • Pain • Rash • Worsening depression • Induction of autoimmunity	• Liver enzymes • CBC with differential • Worsening CHF • Depression, suicidal ideation	Low potential for drug interactions	• The Panel **recommends against** the use of IFNs for the treatment of severely and critically ill COVID-19 patients, except in a clinical trial **(AIII)**. • There are insufficient data to recommend for or against the use of IFN-beta for the treatment of early (i.e., <7 days from symptom onset) mild and moderate COVID-19. • Use with caution with other hepatotoxic agents. • Reduce dose if ALT >5 times ULN. • A list of clinical trials is available: Interferon **Availability:** • Several products are available in the United States; product doses differ. *IFN Beta-1a Products:* • Avonex, Rebif *IFN Beta-1b Products:* • Betaseron, Extavia

Drug Name	Dosing Regimen *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 anakinra 100 mg SQ once daily • Has also been used IV • 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 • Liver enzyme elevations	• CBC with differential • Renal function (reduce dose in patients with CrCl <30 mL/min) • Liver enzymes	Use with TNF-blocking agents **is not recommended** due to increased risk of infection.	• There are insufficient data for the Panel to recommend either 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[15]	**Clinical Trial Dosing (See NCT04315298):** • Sarilumab 400 mg IV (single dose)[16] **Note:** The only FDA-approved sarilumab product is an SQ formulation.	• Neutropenia, thrombocytopenia • Gastrointestinal perforation • HSR • Increased liver enzymes • HBV reactivation • Infusion reaction possible	• Monitor for HSR • Monitor for infusion reaction • Neutrophils • Platelets • Liver enzymes	• 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. • May mask signs of acute inflammation or infection (i.e., suppression of fever and CRP) • A list of clinical trials is available: Sarilumab

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	• Siltuximab 11 mg/kg IV over 1 hour every 3 weeks for multicentric Castleman disease[17] • Dose and duration for COVID-19 unknown	• Infusion-related reaction • HSR • Gastrointestinal perforation • Neutropenia • Hypertension • Dizziness • Rash • Pruritus • Hyperuricemia	• Monitor for HSR • 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. • Effects on CYP450 may persist for weeks after therapy.	• 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 or infection (i.e., suppression of fever and CRP) • A list of clinical trials is available: Siltuximab
Tocilizumab[18]	**Clinical Trial Dosing:** • Tocilizumab 8 mg/kg IV once • Dose **should not exceed** tocilizumab 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 liver enzymes • HBV reactivation	• Monitor for HSR • Monitor for infusion reactions • Neutrophils • Platelets • Liver enzymes	• 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 either for or against the use of tocilizumab for the treatment of COVID-19. • May mask signs of acute inflammation or infection (i.e., suppression of fever and CRP) • SQ formulation **is not intended** for IV administration. • A list of clinical trials is available: Tocilizumab

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
Kinase Inhibitors					
Bruton's Tyrosine Kinase Inhibitors					
Acalabrutinib	**Dose for FDA-Approved Indications:** • Acalabrutinib 100 mg PO every 12 hours • Dose and duration for COVID-19 unknown	• Hemorrhage • Cytopenias (neutropenia, anemia, thrombocytopenia, lymphopenia) • Atrial fibrillation and flutter • Infection • Headache • Diarrhea • Fatigue • Myalgia	• CBC with differential • Signs and symptoms of bleeding (particularly if coadministered with anticoagulant or antiplatelet therapy) • Clinical monitoring for cardiac arrhythmias • Monitor for new infections	• Avoid concomitant use with strong CYP3A inhibitors or inducers. • Dose reduction may be necessary with moderate CYP3A4 inhibitors. • Avoid concomitant PPI use. • H2-receptor antagonist should be administered 2 hours after acalabrutinib.	• The Panel **recommends against** the use of BTK inhibitors for the treatment of COVID-19, except in a clinical trial **(AIII)**. • Avoid in patients with severe hepatic impairment. • Patients with underlying cardiac risk factors, hypertension, or acute infections may be predisposed to atrial fibrillation. • A list of clinical trials is available: Acalabrutinib
Ibrutinib	**Doses for FDA-Approved Indications:** • Ibrutinib 420 mg or 560 mg PO once daily • Dose and duration for COVID-19 unknown	• Hemorrhage • Cardiac arrhythmias • Serious infections • Cytopenias (thrombocytopenia, neutropenia, anemia) • Hypertension • Diarrhea • Musculoskeletal pain • Rash	• CBC with differential • Blood pressure • Signs and symptoms of bleeding (particularly if coadministered with anticoagulant or antiplatelet therapy) • Clinical monitoring for cardiac arrhythmias • Monitor for new infections	• Avoid concomitant use with strong CYP3A inhibitors or inducers. • Dose reduction may be necessary with moderate CYP3A4 inhibitors.	• The Panel **recommends against** the use of BTK inhibitors for the treatment of COVID-19, except in a clinical trial **(AIII)**. • Avoid in patients with severe baseline hepatic impairment. Dose modifications required in patients with mild or moderate hepatic impairment. • Patients with underlying cardiac risk factors, hypertension, or acute infections may be predisposed to cardiac arrhythmias. • A list of clinical trials is available: Ibrutinib

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
Bruton's Tyrosine Kinase Inhibitors, continued					
Zanubrutinib	**Dose for FDA-Approved Indications:** • Zanubrutinib 160 mg PO twice daily or 320 mg PO once daily • Dose and duration for COVID-19 unknown	• Hemorrhage • Cytopenias (neutropenia, thrombocytopenia, anemia, leukopenia) • Atrial fibrillation and flutter • Infection • Rash • Bruising • Diarrhea • Cough • Musculoskeletal pain	• CBC with differential • Signs and symptoms of bleeding • Clinical monitoring for cardiac arrhythmias • Monitor for new infections	• Avoid concomitant use with moderate or strong CYP3A inducers. • Dose reduction required with moderate and strong CYP3A4 inhibitors.	• The Panel **recommends against** the use of BTK inhibitors for the treatment of COVID-19, except in a clinical trial **(AIII)**. • Dose reduction required for severe hepatic impairment. • A list of clinical trials is available: Zanubrutinib
Janus Kinase Inhibitors					
Baricitinib[19]	**For Rheumatoid Arthritis:** • Baricitinib 2 mg PO once daily **Doses for COVID-19 in Clinical Trials:** • Baricitinib 2 mg to 4 mg PO once daily for 7 to14 days	• Lymphoma and other malignancies • Thrombosis • Gastrointestinal perforation • Treatment-related changes in lymphocytes, neutrophils, hemoglobin, liver enzymes • Herpes simplex • Herpes zoster	• CBC with differential • Renal function • Liver enzymes • Monitor for new infections	Dose modification is recommended when concurrently administering with a strong OAT3 inhibitor.	• The Panel **recommends against** the use of JAK inhibitors for the treatment of COVID-19, except in a clinical trial **(AIII)**. • Baricitinib **is not recommended** in patients with severe hepatic or renal impairment. • A list of clinical trials is available: Baricitinib

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
Janus Kinase Inhibitors, continued					
Ruxolitinib	• Doses for FDA-approved indications range from ruxolitinib 5 mg PO twice daily to 20 mg PO twice daily. • Doses in COVID-19 clinical trials range from ruxolitinib 5 mg PO twice daily to 20 mg PO twice daily, for 14 days.	• Thrombocytopenia • Anemia • Neutropenia • Liver enzyme elevations • Risk of infection • Dizziness • Headache • Diarrhea • CPK elevation • Herpes zoster	• CBC with differential • Liver enzymes • Monitor for new infections	• Dose modifications required when administered with strong CYP3A4 inhibitors. • Avoid use with fluconazole doses >200 mg.	• The Panel **recommends against** the use of JAK inhibitors for the treatment of COVID-19, except in a clinical trial **(AIII)**. • Dose modification may be required for moderate and severe renal impairment, hepatic impairment, and thrombocytopenia. • A list of clinical trials is available: Ruxolitinib
Tofacitinib	**Doses for FDA-Approved Indications:** • Tofacitinib 5 mg PO twice daily (rheumatoid and psoriatic arthritis) • Tofacitinib 10 mg PO twice daily (ulcerative colitis) • Dose and duration for COVID-19 unknown; A planned COVID-19 clinical trial will be evaluating 10 mg twice daily for 14 days	• Thrombotic events (pulmonary embolism, DVT, arterial thrombosis) • Anemia • Risk of infection • Gastrointestinal perforation • Diarrhea • Headache • Herpes zoster reactivation • Lipid elevations • Liver enzyme elevations • Lymphoma and other malignancies	• CBC with differential • Liver enzymes • Monitor for new infections	• Dose modifications required when administered with strong CYP3A4 inhibitors, or when used with a moderate CYP3A4 inhibitor coadministered with a strong CYP2C19 inhibitor. • Avoid live vaccines.	• The Panel **recommends against** the use of JAK inhibitors for the treatment of COVID-19, except in a clinical trial **(AIII)**. • Avoid use in patients with ALC <500 cells/mm^3, ANC <1000 cells/mm^3, or Hgb <9 grams/dL. • Dose modification may be required for moderate and severe renal impairment and moderate hepatic impairment. • A list of clinical trials is available: Tofacitinib

Key: AE = adverse effect or adverse event; ALC = absolute lymphocyte count; ALT = alanine transaminase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BTK = Bruton's tyrosine kinase; CBC = complete blood count; CHF = congestive heart failure; CrCl = creatinine clearance; CPK = creatine phosphokinase; CRP = C-reactive protein; CYP = cytochrome P; DVT = deep vein thrombosis; EIND = Emergency Investigational New Drug; FDA = Food and Drug Administration; HBV = hepatitis B; Hgb = hemoglobin; HSR = hypersensitivity reaction; HSV = herpes simplex virus; IFN = interferon; IL-1 = interleukin-1; IL-6 = interleukin-6; IV = intravenous; IVIG = intravenous immunoglobulin; JAK = Janus kinase; MERS = Middle East respiratory syndrome; OAT = organic anion transporter; PO = orally; PPI = proton pump inhibitor; SARS = severe acute respiratory syndrome; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SQ = subcutaneous; TACO = transfusion-associated circulatory overload; TB = tuberculosis; 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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Adjunctive Therapy

Last Updated: July 17, 2020

In addition to the antiviral medications and the immune-based therapies for the treatment of COVID-19 that are discussed elsewhere in the COVID-19 Treatment Guidelines, adjunctive therapies are frequently used in patients with COVID-19 to prevent and/or treat the infection or its complications. Some of these agents are being studied in clinical trials.

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is associated with a prothrombotic state and an increased incidence of thromboembolic disease. Antithrombotic Therapy in Patients with COVID-19 reviews the existing data and provides recommendations for the care of individuals who were receiving antithrombotic agents before they acquired SARS-CoV-2 and those who need these therapies to prevent or treat thromboembolic events during course of the infection.

Some clinicians advocate for the use of vitamin and mineral supplements to treat respiratory viral infections. Multiple ongoing studies are evaluating the use of vitamin and mineral supplements for both the treatment and prevention of SARS-CoV-2 infection.

The following sections describe the underlying rationale for the use of adjunctive therapies and summarize the existing clinical trial data. Additional adjunctive therapies will be added as new evidence emerges.

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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Vitamin C

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Rationale for Using Vitamin C in Patients With COVID-19

Vitamin C (ascorbic acid) is a water-soluble vitamin that is thought to have beneficial effects in patients with severe and critical illnesses. It is an antioxidant and free radical scavenger that has anti-inflammatory properties, influences cellular immunity and vascular integrity, and serves as a cofactor in the generation of endogenous catecholamines.[1,2] Because humans may require more vitamin C in states of oxidative stress, vitamin C supplementation has been evaluated in numerous disease states, including serious infections and sepsis. Because serious COVID-19 may cause sepsis and acute respiratory distress syndrome (ARDS), the potential role of high doses of vitamin C in ameliorating inflammation and vascular injury in patients with COVID-19 is being studied.

Recommendation for Non-Critically Ill Patients With COVID-19

- There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of vitamin C for the treatment of COVID-19 in non-critically ill patients.

Rationale

Because patients who are not critically ill with COVID-19 are less likely to experience oxidative stress or severe inflammation, there is no compelling reason to use vitamin C in this setting.

Recommendation for Critically Ill Patients With COVID-19

- There are insufficient data for the Panel to recommend either for or against the use of vitamin C for the treatment of COVID-19 in critically ill patients.

Rationale

There are no completed controlled trials of vitamin C in patients with COVID-19, and the available observational data are sparse and inconclusive. Studies of vitamin C in sepsis patients and ARDS patients have shown variable efficacy and limited safety concerns (as described below).

Clinical Data on Vitamin C in Critically Ill Patients Without COVID-19

In a small, three-arm, pilot study of two regimens of intravenous (IV) vitamin C versus placebo in 24 critically ill patients with sepsis, there were reductions over the 4-day study period in sequential organ failure assessment (SOFA) scores and levels of proinflammatory markers in patients who received vitamin C 200 mg/kg per day and those who received vitamin C 50 mg/kg per day, compared with patients who received placebo.[3]

In a randomized, controlled trial in critically ill patients with sepsis-induced ARDS (n = 167), administration of IV vitamin C 200 mg/kg per day for 4 days did not change SOFA scores or levels of inflammatory markers. However, 28-day mortality was lower in the treatment group (29.8% vs. 46.3%; $P = 0.03$), coinciding with more days alive and free of the hospital and the intensive care unit (ICU).[4]

Two historically controlled studies found that the combination of vitamin C, thiamine, and hydrocortisone had beneficial effects in patients with sepsis or severe pneumonia.[5,6] In response, a randomized controlled trial in critically ill patients with septic shock compared the combination

of vitamin C (6 g per day), thiamine (400 mg per day), and hydrocortisone (200 mg per day) to hydrocortisone alone. The study reported that the combination therapy had no effect on the duration of shock. It also had no effect on the mortality rate in the ICU, at 28 days, or at 90 days (90-day mortality was 28.6% in the vitamin C group vs. 24.5% in the placebo group, $P = 0.51$). Only one of the 10 secondary outcomes differed between the two groups; the change in SOFA score from baseline to Day 3 favored the treatment group (median score change of -2 vs. -1, $P = 0.02$).[7]

Other Considerations

- It is worth noting that high circulating concentrations of vitamin C may affect the accuracy of point-of-care glucometers.[8]
- Additional large, randomized clinical trials in severely ill patients with sepsis have completed enrollment. These studies may provide additional data on the safety and efficacy of vitamin C that support its potential use in treating patients with COVID-19.[9,10]
- Several trials of oral and IV vitamin C supplementation in people with COVID-19 are ongoing. Please check *ClinicalTrials.gov* for the latest information.

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Vitamin D

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Recommendation

- There are insufficient data to recommend either for or against the use of vitamin D for the prevention or treatment of COVID-19.

General Information

Vitamin D is critical for bone and mineral metabolism. Because the vitamin D receptor is expressed on immune cells such as B cells, T cells, and antigen-presenting cells, and because these cells can synthesize the active vitamin D metabolite, vitamin D also has the potential to modulate innate and adaptive immune responses.[1]

Vitamin D deficiency (defined as a serum concentration of 25-hydroxyvitamin D ≤20 ng/mL) is common in the United States, particularly among persons of Hispanic ethnicity and Black race. These groups are overrepresented among cases of COVID-19 in the United States.[2] Vitamin D deficiency is also more common in older patients and patients with obesity and hypertension; these factors have been associated with worse outcomes in patients with C8OVID-19. In observational studies, low vitamin D levels have been associated with an increased risk of community-acquired pneumonia in older adults[3] and children.[4]

Vitamin D supplements may increase the levels of T regulatory cells in healthy individuals and patients with autoimmune diseases; vitamin D supplements may also increase T regulatory cell activity.[5] In a meta-analysis of randomized clinical trials, vitamin D supplementation was shown to protect against acute respiratory tract infection.[6] However, in two randomized, double-blind, placebo-controlled clinical trials, administering high doses of vitamin D to critically ill patients with vitamin D deficiency (but not COVID-19) did not reduce the length of the hospital stay or the mortality rate when compared to placebo.[7,8] High levels of vitamin D may cause hypercalcemia and nephrocalcinosis.[9]

Vitamin D and COVID-19

The role of vitamin D supplementation in the prevention or treatment of COVID-19 is not known. The rationale for using vitamin D is based largely on immunomodulatory effects that could potentially protect against COVID-19 infection or decrease the severity of illness. Ongoing observational studies are evaluating the role of vitamin D in preventing and treating COVID-19.

Some investigational trials on the use of vitamin D in people with COVID-19 are being planned or are already accruing participants. These trials will administer vitamin D alone or in combination with other agents to participants with and without vitamin D deficiency. The latest information on these clinical trials can be found on *ClinicalTrials.gov*.

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Zinc Supplementation and COVID-19

Last Updated: July 17, 2020

Recommendations

- There are insufficient data to recommend either for or against the use of zinc for the treatment of COVID-19.
- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** using zinc supplementation above the recommended dietary allowance for the prevention of COVID-19, except in a clinical trial **(BIII)**.

Rationale

Increased intracellular zinc concentrations efficiently impair replication in a number of RNA viruses.[1] Zinc has been shown to enhance cytotoxicity and induce apoptosis when used *in vitro* with a zinc ionophore (e.g., chloroquine). Chloroquine has also been shown to enhance intracellular zinc uptake *in vitro*.[2] The relationship between zinc and COVID-19, including how zinc deficiency affects the severity of COVID-19 and whether zinc supplements can improve clinical outcomes, is currently under investigation.[3] Zinc levels are difficult to measure accurately, as zinc is distributed as a component of various proteins and nucleic acids.[4]

Zinc supplementation alone or in combination with hydroxychloroquine for prevention and treatment of COVID-19 is currently being evaluated in clinical trials. The optimal dose of zinc for the treatment of COVID-19 is not established. The recommended dietary allowance for elemental zinc is 11 mg daily for men and 8 mg for nonpregnant women.[5] The doses used in registered clinical trials for COVID-19 vary between studies, with a maximum dose of zinc sulfate 220 mg (50 mg of elemental zinc) twice daily.

Long-term zinc supplementation can cause copper deficiency with subsequent reversible hematologic defects (i.e., anemia, leukopenia) and potentially irreversible neurologic manifestations (i.e., myelopathy, paresthesia, ataxia, spasticity).[6,7] Zinc supplementation for a duration as short as 10 months has been associated with copper deficiency.[8] In addition, oral zinc can decrease the absorption of medications that bind with polyvalent cations.[5] Because zinc has not been shown to have clinical benefit and may be harmful, the Panel **recommends against** using zinc supplementation above the recommended dietary allowance for the prevention of COVID-19, except in a clinical trial **(BIII)**.

Clinical Data

Retrospective Study of Hydroxychloroquine and Azithromycin With or Without Zinc

This study has not been peer-reviewed.

A retrospective observational study compared zinc supplementation to no zinc supplementation in hospitalized patients with COVID-19 who received hydroxychloroquine and azithromycin from March 2 to April 5, 2020. On March 25, the institution's standard of care was updated to include supplementation with zinc sulfate 220 mg orally twice daily. Patients who received any other investigational therapies were excluded. Only patients who were discharged from the hospital, transferred to hospice, or died were included in the analysis. Outcome measures included duration of hospital stay, duration of mechanical ventilation, maximum oxygen flow rate, average oxygen flow rate, average FiO_2, maximum FiO_2, admission to the intensive care unit (ICU), duration of ICU stay, death or transfer to hospice, need for intubation, and discharge destination.[9]

Results

- A total of 932 patients were included in this analysis; 411 patients received zinc, and 521 did not.
- The two groups had similar demographic characteristics.
- Patients who received zinc had higher absolute lymphocyte count and lower troponin and procalcitonin levels at baseline than those who did not receive zinc.
- In univariate analysis, no differences were observed between the two groups in duration of hospital stay, duration of mechanical ventilation, maximum oxygen flow rate, average oxygen flow rate, or average FiO_2.
- In bivariate logistic regression analysis, zinc supplementation was associated with a decreased mortality rate or rate of transfer to hospice; however, the association with a decreased mortality rate was no longer significant when analysis was limited to patients who were treated in the ICU.

Limitations

- This is a retrospective review; patients were not randomized to receive zinc therapy or to receive no zinc. The statistical methods used do not account for confounding variables or patient differences between those who were treated with zinc sulfate and those who were not, with one exception: the authors attempted to account for the change in the institution's treatment standards by using a logistic regression analysis for patients admitted after March 25.
- The preprint did not include specific details on the timing of zinc initiation, and the patients' clinical statuses at the start of therapy were not reported.
- The preprint also did not specify how many patients did or did not receive zinc before and after the institution's treatment standards changed to include zinc sulfate on March 25. The authors used a logistic regression analysis to account for this, as discussed above.
- Only patients who died or who were transferred to hospice or discharged are included in the analyses. The exclusion of those who were still hospitalized as of April 5 makes it difficult to compare the clinical outcomes for those who received or did not receive zinc sulfate.

Given the nature of the study design and its limitations, the authors do not recommend using this study to guide clinical practice.

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Considerations for Certain Concomitant Medications in Patients with COVID-19

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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, except in 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) for the treatment of COVID-19 in patients who are mechanically ventilated **(AI)** and in patients who require supplemental oxygen but who are not mechanically ventilated **(BI)**. • The Panel **recommends against** using **dexamethasone** for the treatment of COVID-19 in patients who do not require supplemental oxygen **(AI)**. • See Corticosteroids (Including 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)**. *Considerations in pregnancy* • Given the potential benefit of decrease in maternal mortality and the low risk of fetal adverse effects for this short course of therapy, the Panel recommends using **dexamethasone** in pregnant women with COVID-19 who are mechanically ventilated **(AIII)** or who require supplemental oxygen but who are not mechanically ventilated **(BIII)**. **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, except in 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, except in 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 ACE inhibitors or ARBs could suppress or enhance SARS-CoV-2 replication.[2] Investigations of the role of ARBs and recombinant human ACE2 in the 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. The Panel's recommendation against the use of these medications for the treatment of COVID-19 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 reported for 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 SARS), corticosteroid therapy was associated with delayed virus clearance. In severe pneumonia caused by influenza, corticosteroid therapy may lead to worse 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

Recommendations

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

See Corticosteroids (Including 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

A short course of betamethasone and dexamethasone, which are corticosteroids known to cross the placenta, is routinely used to hasten fetal lung maturity and decrease the risk of neonatal respiratory distress syndrome in the premature infant with threatened delivery.[10,11]

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

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, except in a clinical trial **(AIII)**.

HMG-CoA reductase inhibitors, or statins, affect ACE2 as part of their function in reducing endothelial dysfunction. It has been proposed that these agents have a potential role in managing patients with severe COVID-19.[12] 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 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)**.

In mid-March 2020, news agencies promoted reports that anti-inflammatory drugs may worsen COVID-19. It has been proposed that NSAIDs such as ibuprofen can increase the expression of ACE2[1] and inhibit antibody production.[13] 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.[14]

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Special Populations

To date, the vast majority of the data generated about the epidemiology, clinical course, prevention, and treatment of COVID-19 have come from studies of nonpregnant adults. More information is urgently needed for other populations, such as pediatric patients, pregnant patients, transplant patients, and other immunocompromised patients with COVID-19.

Children with COVID-19 may have less severe disease overall when compared to adults, but the recently described multisystem inflammatory syndrome in children (MIS-C) requires further study. Data are also emerging on the clinical course of COVID-19 in pregnant patients, pregnancy outcomes in the setting of COVID-19, and vertical transmission of severe acute respiratory coronavirus 2, but further research is needed. There are special considerations for transplant recipients, cancer patients, and patients with other immunocompromising conditions (e.g., rheumatologic conditions, inflammatory bowel disease), as they may be at increased risk of serious complications and death as a result of COVID-19.

The following sections review and synthesize the available data for some of these populations and discuss the specific considerations that clinicians should take into account when caring for these patients.

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

Last Updated: July 17, 2020

Summary Recommendations
Potential Transplant and Cellular Therapy Candidates • The COVID-19 Treatment Guidelines Panel (the Panel) recommends diagnostic molecular testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) for all potential solid organ transplant (SOT), hematopoietic cell transplant (HCT), and cell therapy candidates with signs and symptoms that suggest acute COVID-19 infection **(AIII)**. • The Panel recommends following the guidance from medical professional organizations that specialize in providing care for SOT, HCT, or cell therapy recipients when performing diagnostic molecular testing for SARS-CoV-2 in these patients **(AIII)**. • If SARS-CoV-2 is detected or if infection is strongly suspected, transplantation should be deferred, if possible **(BIII)**.

Potential Transplant Donors
• The Panel recommends assessing all potential SOT donors for signs and symptoms that are associated with COVID-19 according to guidance from medical professional organizations **(AIII)**.
  • The Panel recommends performing diagnostic molecular testing for SARS-CoV-2 if symptoms are present **(AIII)**.
  • If SARS-CoV-2 is detected or if infection is strongly suspected, donation should be deferred **(BIII)**.
• The Panel recommends assessing all potential HCT donors for signs and symptoms that are associated with COVID-19 according to guidance from medical professional organizations **(AIII)**.
  • The Panel recommends performing diagnostic molecular testing for SARS-CoV-2 when symptoms are present **(AIII)**.
  • If SARS-CoV-2 is detected or if infection is strongly suspected, donation should be deferred **(BIII)**.

Transplant and Cellular Therapy Recipients with COVID-19 • Clinicians should follow the guidelines for evaluating and managing COVID-19 in nontransplant patients when treating transplant and cellular therapy recipients **(AIII)**. See Management of Persons with COVID-19, Potential Antiviral Drugs Under Evaluation for the Treatment of COVID-19, and Immune-Based Therapy Under Evaluation for Treatment of COVID-19 for more information. • The Panel recommends that clinicians who are treating COVID-19 in transplant and cellular therapy patients consult with a transplant specialist before adjusting immunosuppressive medications **(AIII)**. • When treating COVID-19, clinicians should pay careful attention to potential drug-drug interactions and overlapping toxicities with immunosuppressants, prophylactic antimicrobials, and other medications **(AIII)**.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional **Rating of Evidence:** I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion

Introduction

Treating COVID-19 in solid organ transplant (SOT), hematopoietic cell transplant (HCT), and cellular immunotherapy recipients can be challenging due to the presence of coexisting medical conditions, transplant-related cytopenias, and the need for chronic immunosuppressive therapy to prevent graft rejection and graft-versus-host disease. Transplant recipients may also potentially have increased exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) given their frequent contact with the health care system. Since immunosuppressive agents modulate several aspects of the host's immune response, the severity of COVID-19 could potentially be affected by the type and the intensity

of the immunosuppressive effect of the agent, as well as by specific combinations of immunosuppressive agents. Some transplant recipients have medical comorbidities that have been associated with more severe cases of COVID-19 and a greater risk of mortality, which makes the attributable impact of transplantation on disease severity difficult to assess.

The American Association for the Study of Liver Diseases (AASLD),[1] the International Society for Heart and Lung Transplantation, the American Society of Transplantation, the American Society for Transplantation and Cellular Therapy (ASTCT), the European Society for Blood and Marrow Transplantation (EBMT), and the Association of Organ Procurement Organizations provide guidance for clinicians who are caring for transplant recipients with COVID-19, as well as guidance for screening potential donors and transplant or cell therapy candidates. This section of the Guidelines complements these sources and focuses on considerations for managing COVID-19 in SOT, HCT, and cellular therapy recipients. The optimal management and therapeutic approach to COVID-19 in these populations is unknown. At this time, the procedures for evaluating and managing COVID-19 in transplant recipients are the same as for nontransplant patients **(AIII)**. See Management of Persons with COVID-19, Potential Antiviral Drugs Under Evaluation for the Treatment of COVID-19, and Immune-Based Therapy Under Evaluation for Treatment of COVID-19 for more information. The medications that are used to treat COVID-19 may present different risks and benefits to transplant patients and nontransplant patients.

Assessment of SARS-CoV-2 Infection in Transplant and Cellular Therapy Candidates and Donors

The risk of transmission of SARS-CoV-2 from donors to candidates is unknown. The probability of donor or candidate infection with SARS-CoV-2 may be estimated by considering epidemiologic risk, obtaining clinical history, and testing with molecular techniques. No current testing strategy is sensitive enough or specific enough to totally exclude active infection. Living solid organ donors should be counseled on strategies to prevent infection and monitored for exposures and symptoms in the 14 days prior to scheduled transplant.[2] HCT donors should practice good hygiene and avoid crowded places and large group gatherings during the 28 days prior to donation.[3]

Assessment of Transplant and Cellular Therapy Candidates

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

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

Assessment of Donors

The COVID-19 Treatment Guidelines Panel (the Panel) recommends following the guidance from medical professional organizations and assessing all potential HCT donors for exposure to COVID-19 and clinical symptoms that are compatible with COVID-19 before donation **(AIII)**. Deceased donors should undergo screening for known symptoms and exposure to others with COVID-19 before transplantation, and decisions about using such organs should be made on a case-by-case basis **(BIII)**. Recommendations for screening are outlined in the ASTCT and EBMT guidelines.

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

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

Transplant Recipients with COVID-19

SOT recipients who are receiving immunosuppressive therapy should be considered to be at increased risk for severe COVID-19.[1,4] A national survey of 88 U.S. transplant centers conducted between March 24 and 31, 2020, reported that 148 SOT recipients received a diagnosis of COVID-19 infection (69.6% were kidney recipients, 15.5% were liver recipients, 8.8% were heart recipients, and 6.1% were lung recipients).[5] COVID-19 was mild in 54% of recipients and moderate in 21% of recipients, and 25% of recipients were critically ill. Modification of immunosuppressive therapy during COVID-19 and the use of investigational therapies for treatment of COVID-19 varied widely among recipients. Initial reports of transplant recipients who were hospitalized with COVID-19 suggest mortality rates of up to 28%.[6-9]

Risk of Graft Rejection

There have been no published reports of graft rejection in SOT recipients who received a diagnosis of COVID-19, although this may be due to a limited ability to perform biopsies. Acute cellular rejection should not be presumed in SOT recipients without biopsy confirmation in individuals with or without COVID-19. Similarly, immunosuppressive therapy should be initiated in recipients with or without COVID-19 who have rejection confirmed by a biopsy.[1]

There is a lack of data on the incidence and clinical characteristics of SARS-CoV-2 infection in HCT and cellular therapy recipients. Experience with other respiratory viruses suggests that this population is at a high risk for severe disease, including increased rates of lower respiratory tract infection and mortality.[10] Factors that may determine clinical severity include degree of cytopenia, time since transplant, intensity of the conditioning regimen, graft source, degree of mismatch, and the need for further immunosuppression to manage graft-versus-host disease. For other respiratory viruses, HCT recipients often exhibit prolonged viral shedding,[11-14] which can have implications for infection prevention and for the timing of potential interventions.

Treatment of COVID-19 in Transplant Recipients

Currently, no drug has been approved by the Food and Drug Administration (FDA) for the treatment of COVID-19, although preliminary data suggest that the investigational antiviral drug remdesivir can be used in those with severe disease. Remdesivir is available for use in these patients under the FDA's Emergency Use Authorization.[15]

Preliminary data from a large randomized controlled trial have shown that a short course of dexamethasone (6 mg once daily for up to 10 days) can improve survival in patients with COVID-19 who are mechanically ventilated or who require supplemental oxygen.[16] At this time, the risks and benefits of using dexamethasone in transplant recipients with COVID-19 who are receiving immunosuppressive therapy, which may include corticosteroids, are unknown.

The Panel's recommendations for the use of remdesivir and dexamethasone in patients with COVID-19 can be found in the Remdesivir and Corticosteroids sections.

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

The use of antiviral or immune-based therapies for the treatment of COVID-19 can present additional challenges in transplant patients. Clinicians should pay special attention to the potential for drug-drug interactions and overlapping toxicities with concomitant medications, such as immunosuppressants that are used to prevent allograft rejection (e.g., corticosteroids, mycophenolate, and calcineurin inhibitors such as tacrolimus and cyclosporine), antimicrobials that are used to prevent opportunistic infections, and other medications. Dose modifications may be necessary for drugs that are used to treat COVID-19 in transplant recipients with pre-existing organ dysfunction. Adjustments to the immunosuppressive regimen should be individualized based on disease severity, the specific immunosuppressants used, the type of transplant, the time since transplantation, the drug concentration, and the risk of graft rejection.[7] Clinicians who are treating COVID-19 in transplant patients should consult with a transplant specialist before adjusting immunosuppressive medication **(AIII)**.

Certain investigational or off-label therapeutics (e.g., remdesivir, tocilizumab) are associated with elevated levels of transaminases. For liver transplant recipients, the AASLD does not view abnormal liver biochemistries as a contraindication to using investigational or off-label therapeutics, although certain elevation thresholds may exclude patients from trials of some investigational agents.[17] Close monitoring of liver biochemistries is warranted in patients with COVID-19, especially when they are receiving agents with a known risk of hepatotoxicity.

Calcineurin inhibitors, which are commonly used to prevent allograft rejection, have a narrow therapeutic index. Medications that inhibit or induce cytochrome P450 enzymes or P-glycoprotein may put patients who receive calcineurin inhibitors at risk of clinically significant drug-drug interactions, increasing the need for therapeutic drug monitoring and the need to assess for signs of toxicity or rejection.[18] Similarly, transplant patients may be at a higher risk of adverse effects, particularly when their concomitant medications have overlapping toxicities. Specific concerns about the use of potential antiviral medications and immune-based therapy for COVID-19 in transplant patients are noted below. See Tables 2b and 3b for additional details.

Table 4. Special Concerns for Drugs That Are Being Evaluated for COVID-19 Treatment in Transplant Patients

Last Updated: July 17, 2020

Drugs That Are Being Evaluated for COVID-19 Treatment	Concerns in Transplant Patients
Azithromycin	• Hepatotoxicity (cholestatic hepatitis, rare) • Additive effect with other drugs that prolong the QTc interval.
Chloroquine and Hydroxychloroquine	• Moderate inhibition of CYP2D6. • Inhibition of P-gp may increase levels of calcineurin inhibitors and mTOR inhibitors. • Additive effect with other drugs that prolong the QTc interval.
Dexamethasone	• Moderate CYP3A4 inducer • Potential for additional immunosuppression and increased risk of OIs.
HIV Protease Inhibitors	• RTV and other PIs are strong inhibitors of CYP3A4. Coadministration will increase concentrations of tacrolimus, cyclosporine, everolimus, sirolimus, and prednisone. • TDM and dose adjustment of immunosuppressant is necessary. Monitor for calcineurin inhibitor-associated toxicities.
Interleukin-6 Inhibitors	• Use of IL-6 inhibitors may lead to increased metabolism of drugs that are CYP substrates. Effects on CYP may persist for weeks after therapy. • AEs include neutropenia and an increase in transaminases. See Table 3b.
Remdesivir	• Strong P-gp inducers (e.g., rifampin) may reduce RDV exposure. Coadministration **is not recommended**. • Increase in levels of serum transaminases. • Accumulation of drug vehicle cyclodextrin in patients with kidney dysfunction.
Ribavirin	• Significant toxicities, including anemia, bradycardia, and an increase in serum transaminases levels.

Key: AE = adverse effects; CYP = cytochrome P450; IL = interleukin; mTOR = mechanistic target of rapamycin; OI = opportunistic infection; P-gp = P-glycoprotein; PI = protease inhibitor; RDV = remdesivir; RTV= ritonavir; TDM = therapeutic drug monitoring

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

Last Updated: June 11, 2020

Name	Affiliation
Co-Chairs	
Roy M. Gulick, MD, MPH	Weill Cornell Medicine, New York, NY
H. Clifford Lane, MD	National Institutes of Health, Bethesda, MD
Henry Masur, MD	National Institutes of Health, Bethesda, MD
Executive Secretary	
Alice K. Pau, PharmD	National Institutes of Health, Bethesda, MD
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David V. Glidden, PhD	University of California San Francisco, San Francisco, CA
Birgit Grund, PhD	University of Minnesota, Minneapolis, MN
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Marla J. Keller, MD	Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY
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Jeffrey L. Lennox, MD	Emory University School of Medicine, Atlanta, GA
Mitchell M. Levy, MD	Warren Alpert Medical School of Brown University, Providence, RI
Gregory Martin, MD, MSc	Emory University School of Medicine, Atlanta, GA
Susanna Naggie, MD, MHS	Duke University School of Medicine, Durham, NC
Andrew T. Pavia, MD	University of Utah School of Medicine, Salt Lake City, UT
Nitin Seam, MD	National Institutes of Health, Bethesda, MD
Steven Q. Simpson, MD	University of Kansas Medical Center, Kansas City, KS
Susan Swindells, MBBS	University of Nebraska Medical Center, Omaha, NE

Name	Affiliation
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Pablo Tebas, MD	University of Pennsylvania, Philadelphia, PA
Phyllis Tien, MD, MSc	University of California, San Francisco/San Francisco VA Healthcare System, San Francisco, CA
Alpana A. Waghmare, MD	Seattle Children's Hospital, Seattle, WA
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
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Assistant Executive Secretaries	
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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
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	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