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/).

Credit NIAID-RML

Table of Contents

What's New in the Guidelines

(Last updated May 12, 2020)

New Section of the Guidelines

Antithrombotic Therapy in Patients with COVID-19

COVID-19 has been associated with inflammation and a prothrombotic state, with increases in fibrin, fibrin degradation products, fibrinogen, and D-dimers. Although the true incidence of thrombosis is unknown, there have been reports of increased incidence of thromboembolic disease associated with COVID-19 in patients in the intensive care unit.

A new section titled Antithrombotic Therapy in Patients with COVID-19 has been added to the guidelines to address many questions related to the role of coagulation markers and thrombolytic, anticoagulant, and antiplatelet agents in those with COVID-19. In this section, the COVID-19 Treatment Guidelines Panel (the Panel) provides recommendations on the use of antithrombotic agents for the prevention of venous thromboembolic events in hospitalized patients with COVID-19. In addition, the Panel recommends carefully monitoring, evaluating, and treating hospitalized patients with COVID-19 for incident thrombotic events when indicated.

Updates to the Guidelines

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

Throughout the section, study descriptions were updated to clearly indicate a study's publication status and to provide an assessment of a study's limitations and results. Data were also updated as needed based on changes to preprints or post-publication changes.

The following recommendations were added or revised in this section:

Remdesivir:

- On the basis of preliminary clinical trial data, the Panel recommends the investigational antiviral agent remdesivir for the treatment of COVID-19 in hospitalized patients with severe disease, defined as SpO_2 ≤94% on ambient air (at sea level), requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation **(BI)**.

  - Remdesivir is not approved by the Food and Drug Administration (FDA); however, it is available through an FDA emergency use authorization for the treatment of hospitalized adults and children with COVID-19. Remdesivir is also being investigated in clinical trials, and it is available through an emergency access program for children and pregnant patients.

- The Panel **does not recommend** remdesivir for the treatment of mild or moderate COVID-19 outside the setting of a clinical trial **(AIII)**.

Chloroquine/Hydroxychloroquine:

- The Panel **recommends against** using **high-dose chloroquine** (600 mg twice daily for 10 days) for the treatment of COVID-19 **(AI)**, because the high dose carries a higher risk of toxicities than the lower dose.

- The FDA warning that cautioned against the use of chloroquine or hydroxychloroquine for COVID-19 outside the setting of a hospital or clinical trial was added to this section.

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

The following key changes were made to this section:

Convalescent Plasma and Immune Globulins:

- New information has been added to the section on convalescent plasma and SARS-CoV-2-specific immune globulins.

- A new section for non-SARS-CoV-2 intravenous immune globulin (IVIG) was created, in which the Panel **recommends against** the use of **non-SARS-CoV-2-specific IVIG** for the treatment of COVID-19, except in the context of a clinical trial **(AIII)**. This should not preclude the use of IVIG when it is otherwise indicated for the treatment of complications that arise during the course of COVID-19.

Interleukin-6 Inhibitors:

- New data from an interim review of a Phase 2/3 clinical trial for sarilumab have been included.

- New preliminary results from a clinical trial for tocilizumab (CORIMUNO-TOCI) have been added.

- There is no change to the Panel's recommendation for IL-6 inhibitors. There are insufficient data to recommend either for or against the use of **IL-6 inhibitors** (e.g., **sarilumab**, **siltuximab**, **tocilizumab**) for the treatment of COVID-19 **(AIII)**.

Introduction

(Last updated May 12, 2020)

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

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

Panel Composition

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

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

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

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

Development of the Guidelines

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

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

Each Guideline section has been reviewed, modified as necessary, and voted on by the entire Panel. A majority vote was required for a recommendation to be included in the posted Guidelines. Panel members are required to keep all Panel deliberations and unpublished data considered during the development of the Guidelines confidential.

Method of Synthesizing Data and Formulating Recommendations

The working groups critically review and synthesize the available data to develop recommendations. Aspects of the data that are considered include, but are not limited to, the type of study (e.g., case series, prospective cohort, randomized controlled trial), the quality and suitability of the methods, the number of participants, and the effect sizes observed. Each recommendation is assigned two ratings according to the scheme presented in Table 1.

Table 1. Recommendation Rating Scheme

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement **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 relied heavily on experience with other diseases, supplemented with evolving personal clinical experience with COVID-19, and incorporated the rapidly growing published scientific literature on COVID-19. When information existed in other published guidelines that the Panel felt important to include in these Guidelines, the information was included with permission from the original sources.

Evolving Knowledge on Treatment for COVID-19

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

For this reason, whenever possible, the Panel recommends that promising, unapproved or unlicensed treatments for COVID-19 be studied in well-designed controlled clinical trials. This includes drugs that have been approved or licensed for other indications. The Panel recognizes the critical importance of clinical research in generating evidence to address unanswered questions regarding the safety and efficacy of potential treatments for COVID-19. However, the Panel also realizes that many patients and providers who cannot access such trials are still seeking guidance about whether to use these agents.

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

Overview and Spectrum of COVID-19

(Last updated April 21, 2020)

Summary Recommendations
• The COVID-19 Treatment Guidelines Panel (the Panel) **does not recommend** the use of any agents for pre-exposure prophylaxis (PrEP) against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outside of the setting of a clinical trial **(AIII)**.
• The Panel **does not recommend** the use of any agents for post-exposure prophylaxis (PEP) against SARS-CoV-2 infection outside of the setting of a clinical trial **(AIII)**.
• 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)**.
• At present, no drug has been proven to be safe and effective for treating COVID-19. There are insufficient data to recommend either for or against the use of any antiviral or immunomodulatory therapy in patients with COVID-19 who have mild, moderate, severe, or critical illness **(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

Epidemiology

The COVID-19 pandemic has exploded since cases were first reported in China in January 2020. As of April 19, 2020, more than 2.4 million cases of COVID-19—caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection—have been reported globally, including >165,000 deaths. Cases have been reported in more than 180 countries, including all 50 states of the United States.[1,2]

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

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

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

Clinical Presentation

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

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

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

Diagnosis of SARS-CoV-2 Infection

Ideally, diagnostic testing would be conducted for all patients with a syndrome consistent with COVID-19, people with known high-risk exposures, and 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.

CDC recommends that nasopharynx samples be used to detect SARS-CoV-2. Nasal swabs or oropharyngeal swabs may be acceptable alternatives.[12] Lower respiratory tract samples have a higher yield than upper tract samples, but often they are not obtained because of concerns about aerosolization of virus during sample collection procedures.

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. More than 20 diagnostic tests for SARS-CoV-2 infection have received Emergency Use Authorization by the Food and Drug Administration.[13] Formal comparisons of these tests are in progress.

CDC has established a priority system for diagnostic testing for SARS-CoV-2 infection based on the availability of tests;[14] the CDC testing guidance is updated periodically.

- *Priority 1:* Hospitalized patients and symptomatic health care workers (to reduce the risk of nosocomial infections and maintain the health care system).
- *Priority 2:* Individuals with symptoms who live in long-term care facilities, who are aged ≥65 years, or who have underlying conditions, and symptomatic first responders (to ensure those at highest risk of complications of infection are rapidly identified and triaged).
- *Priority 3:* In communities experiencing high COVID-19 hospitalizations, critical infrastructure workers and other individuals with symptoms, health care workers and first responders, and individuals with mild symptoms (to decrease community spread and ensure the health of essential workers).

Of note, false-negative test results can occur. In people with a high likelihood of infection based on exposure history and/or clinical presentation, a single negative test does not completely exclude SARS-CoV-2 infection, and testing should be repeated.

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

The onset and duration of viral shedding and period of infectiousness are not completely defined. Asymptomatic or pre-symptomatic individuals infected with SARS-CoV-2 may have viral RNA detected in upper respiratory specimens before the onset of symptoms.[15] Transmission of SARS-CoV-2 from asymptomatic individuals has been described.[16-18] The extent to which this occurs remains unknown.

References

1. World Health Organization. Coronavirus disease (COVID-2019) situation reports. 2020. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/. Accessed April 9, 2020.

2. Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19): cases in U.S. 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html. Accessed April 9, 2020.

3. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32167524.

4. Guan WJ, Ni ZY, Hu Y, et al. Characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32109013.

5. Cai Q, Chen F, Luo F, et al. Obesity and COVID-19 severity in a designated hospital in Shenzhen, China. *Preprints with the Lancet*. 2020. [Preprint]. Available at: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3556658.

6. Centers for Disease Control and Prevention. People Who Are at Higher Risk for Severe Illness. 2020; https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-at-higher-risk.html. Accessed April 8, 2020.

7. Garg S, Kim L, Whitaker M, et al. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019 - COVID-NET, 14 states, March 1-30, 2020. *MMWR Morb Mortal Wkly Re*p. 2020;69(15):458-464. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32298251.

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

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

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

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

12. Centers for Disease Control and Prevention. Interim guidelines for collecting, handling, and testing clinical specimens from persons for coronavirus disease 2019 (COVID-19). 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/lab/guidelines-clinical-specimens.html. Accessed April 8, 2020.

13. Food and Drug Administration. Coronavirus disease 2019 (COVID-19) emergency use authorizations for medical devices. 2020. Available at: https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations#covid19ivd. Accessed April 8, 2020.

14. Centers for Disease Control and Prevention. Evaluating and testing persons for coronavirus disease 2019 (COVID-19). 2020. Available at: https://www.cdc.gov/coronavirus/2019-nCoV/hcp/clinical-criteria.html. Accessed April 8, 2020.

15. Pan Y, Zhang D, Yang P, Poon LLM, Wang Q. Viral load of SARS-CoV-2 in clinical samples. *Lancet Infect Dis*. 2020;20(4):411-412. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32105638.

16. Rothe C, Schunk M, Sothmann P, et al. Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. *N Engl J Med*. 2020;382(10):970-971. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32003551.

17. Yu P, Zhu J, Zhang Z, Han Y, Huang L. A familial cluster of infection associated with the 2019 novel coronavirus indicating potential person-to-person transmission during the incubation period. *J Infect Dis*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32067043.

18. Bai Y, Yao L, Wei T, et al. Presumed asymptomatic carrier transmission of COVID-19. *JAMA*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32083643.

Persons at Risk for Infection with SARS-CoV-2

(Last updated April 21, 2020)

Pre-Exposure Prophylaxis

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

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

Post-Exposure Prophylaxis

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

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

Management of Persons with COVID-19

(Last updated April 21, 2020)

Patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can experience a range of clinical manifestations, from no symptoms to critical illness. This section discusses the clinical management of patients according to the severity of their illness. Currently, no Food and Drug Administration (FDA)-approved drugs exist to specifically treat patients with COVID-19. Chloroquine and hydroxychloroquine, which are not FDA approved for COVID-19, are available from the Strategic National Stockpile for hospitalized adults and adolescents (weighing ≥50 kg) under an Emergency Use Authorization. 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 expanded access or compassionate use mechanisms. Available clinical data for these drugs under investigation are discussed in the Antiviral Therapy and Immune-Based Therapy sections of these Guidelines. **As noted in that section, no drug has been proven to be safe and effective for the treatment of COVID-19.**

In general, patients with COVID-19 can be grouped into the following illness categories:

- *Asymptomatic or Presymptomatic Infection:* Individuals who test positive for SARS-CoV-2 but have no symptoms
- *Mild Illness:* Individuals who have any of various signs and symptoms (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnea, or abnormal imaging
- *Moderate Illness:* Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO_2) >93% on room air at sea level
- *Severe Illness:* Individuals who have respiratory frequency >30 breaths per minute, SpO_2 ≤93% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300, or lung infiltrates >50%
- *Critical Illness:* Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction

Asymptomatic or Presymptomatic Infection

Asymptomatic infection can occur, although the percentage of patients who remain truly asymptomatic for the course of their infection is unknown. 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. Eventually, the availability of widespread testing for SARS-CoV-2 and the development of 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 and who are asymptomatic should self-isolate. If they remain asymptomatic, they can discontinue isolation 7 days after the date of their first positive SARS-CoV-2 test.[2] Individuals who become symptomatic should contact their health care provider for further guidance. Health care workers who test 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.

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 any of various signs and symptoms (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath or dyspnea 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 immuno–modulatory therapy in patients COVID-19 with mild illness (AIII).

Moderate Illness

Moderate COVID-19 illness is defined as evidence of lower respiratory disease by clinical assessment or imaging with SpO_2 >93% on room air at sea level. Given that pulmonary disease can rapidly progress in patients with COVID-19, patients with moderate COVID-19 should be admitted to a health care facility for close observation. 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.

Most patients with moderate to severe illness will require hospitalization. Hospital infection prevention and control measures include use of personal protective equipment (PPE) for droplet and contact precautions (e.g., masks, face shields, gloves, gowns), including eye protection (e.g., face shields or goggles) 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, confirmed COVID-19 patients 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 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, 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.

There are insufficient data for the Panel to recommend either for or against any antiviral or immunomodulatory therapy in patients with COVID-19 with moderate illness (AIII).

Clinicians can refer to the Antiviral Therapy and Immune-Based Therapy sections and Tables 2a and 3a of these guidelines to review the available clinical data regarding investigational drugs being evaluated for treatment of this disease.

Severe Illness

Patients with COVID-19 are considered to have severe illness if they have SpO_2 ≤93% on room air at sea level, respiratory rate >30, PaO_2/FiO_2 <300, 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 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 CBC with differential and 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.

There are insufficient data for the Panel to recommend either for or against any antiviral or immunomodulatory therapy in patients with COVID-19 with severe illness (AIII).

Clinicians can refer to the Antiviral Therapy and Immune-Based Therapy sections and Tables 2a and 3a of these guidelines to review the available clinical data regarding drugs being evaluated for treatment of this disease.

Critical Illness (For additional details, see Care of Critically Ill Patients with COVID-19.)

COVID-19 is primarily a pulmonary disease. Severe cases may be associated with acute respiratory distress syndrome (ARDS), 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 co-morbidities. In addition to pulmonary disease, patients with COVID-19 may also experience cardiac, hepatic, renal, and central nervous system disease.

Since 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 acknowledge 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.

There are insufficient data for the Panel to recommend either for or against any antiviral or immunomodulatory therapy in critically ill patients with COVID-19 (AIII).

Clinicians can refer to the Antiviral Therapy and Immune-Based Therapy sections and Tables 2a and 3a of these guidelines to review the available clinical data regarding drugs being evaluated for treatment of this disease.

References

1. Wang Y, Liu Y, Liu L, Wang X, Luo N, Ling L. Clinical outcome of 55 asymptomatic cases at the time of hospital admission infected with SARS-coronavirus-2 in Shenzhen, China. *J Infect Dis*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32179910.

2. Centers for Disease Control and Prevention. Discontinuation of isolation for persons with COVID-19 not in healthcare settings (interim guidance). 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-in-home-patients.html. Accessed April 8, 2020.

3. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32109013.

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

5. Centers for Disease Control and Prevention. Interim infection prevention and control recommendations for patients with suspected or confirmed coronavirus disease 2019 (COVID-19) in healthcare settings. 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/infection-control/control-recommendations.html. Accessed April 8, 2020.

6. Centers for Disease Control and Prevention. Strategies to optimize the supply of PPE and equipment. 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/ppe-strategy/index.html. Accessed April 8, 2020.

7. Centers for Disease Control and Prevention. Approved respirator standards. 2006. Available at: https://www.cdc.gov/niosh/npptl/standardsdev/cbrn/papr/default.html. Accessed April 8, 2020.

8. Alhazzani W, Moller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). *Crit Care Med*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32224769.

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]

References

1. Centers for Disease Control and Prevention. Interim considerations for infection prevention and control of coronavirus disease 2019 (COVID-19) in inpatient obstetric healthcare settings. 2020. https://www.cdc.gov/coronavirus/2019-ncov/hcp/inpatient-obstetric-healthcare-guidance.html. Accessed April 2, 2020.

2. The American College of Obstetricians and Gynecologists. Practice advisory: novel coronavirus 2019 (COVID-19). https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2020/03/novel-coronavirus-2019.

3. Society for Maternal Fetal Medicine. Coronavirus (COVID-19) and pregnancy: what maternal fetal medicine subspecialists need to know. 2020. https://www.smfm.org/covid19. Accessed April 8, 2020.

4. Rasmussen SA, Smulian JC, Lednicky JA, Wen TS, Jamieson DJ. Coronavirus disease 2019 (COVID-19) and pregnancy: what obstetricians need to know. *Am J Obstet Gynecol*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32105680.

5. Chen H, Guo J, Wang C, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet*. 2020;395(10226):809-815. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32151335.

6. Liu Y, Chen H, Tang K, Guo Y. Clinical manifestations and outcome of SARS-CoV-2 infection during

pregnancy. *J Infect*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32145216.

7. Breslin N, Baptiste C, Miller R, et al. COVID-19 in pregnancy: early lessons. *American Journal of Obstetrics & Gynecology MFM*. 2020. [In Press]. Available at: https://www.sciencedirect.com/science/article/pii/S2589933320300410?via%3Dihub.

8. World Health Organization. Report of the WHO-China joint mission on coronavirus disease 2019 (COVID-19). 2020; https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf. Accessed March 27, 2020.

9. Breslin N, Baptiste C, Gyamfi-Bannerman C, et al. COVID-19 infection among asymptomatic and symptomatic pregnant women: Two weeks of confirmed presentations to an affiliated pair of New York City hospitals. *Am J Obstet Gynecol MFM*. 2020:100118. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32292903.

10. The American College of Obstetricians and Gynecologists. Outpatient assessment and management for pregnant women with suspected or confirmed novel coronavirus (COVID-19). 2020; https://www.smfm.org/covid19/. Accessed April 2, 2020.

11. The American College of Obstetricians and Gynecologists. COVID-19 frequently asked questions for obstetricians-gynecologists, obstetrics. 2020. https://www.acog.org/clinical-information/physician-faqs/covid-19-faqs-for-ob-gyns-obstetrics. Accessed April 2, 2020.

Special Considerations in Children

(Last updated April 21, 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 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.[1-6] Preliminary data from the Centers for Disease Control and Prevention 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.[7-9]

No specific data are available establishing 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. 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.

As above, there is insufficient data to recommend for or against the use of specific antivirals or immunomodulatory agents for the treatment of COVID-19 in pediatric patients. Disease classifications outlined in this document primarily focus on COVID-19 in adults. Several different classification schemes have been used to stratify patients with COVID-19 and other respiratory infections based on illness severity and/or primary site of infection. 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 if trials are available.

A number of 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 for dosing recommendations in children.

References

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

2. Cui Y, Tian M, Huang D, et al. A 55-day-old female infant infected with COVID 19: presenting with pneumonia, liver injury, and heart damage. *J Infect Dis*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32179908.

3. Cai J, Xu J, Lin D, et al. A Case Series of children with 2019 novel coronavirus infection: clinical and epidemiological features. *Clin Infect Dis*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32112072.

4. Kam KQ, Yung CF, Cui L, et al. A well infant with coronavirus disease 2019 (COVID-19) with high viral load. *Clin Infect Dis*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32112082.

5. Dong Y, Mo X, Hu Y, et al. Epidemiological characteristics of 2,143 pediatric patients with 2019 coronavirus disease in China. *Pediatrics*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32179660.

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

7. Chen H, Guo J, Wang C, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet*. 2020;395(10226):809-815. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32151335.

8. Fan C, Lei D, Fang C, et al. Perinatal transmission of COVID-19 associated SARS-CoV-2: should we worry? *Clin Infect Dis*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32182347.

9. Zeng L, Xia S, Yuan W, et al. Neonatal early-onset infection with SARS-CoV-2 in 33 neonates born to mothers with COVID-19 in Wuhan, China. *JAMA Pediatr*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32215598.

Care of Critically Ill Patients with COVID-19

(Last updated May 12, 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 done 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)**.

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 in the event intubation becomes necessary, that the procedure be performed by an experienced practitioner in a controlled setting **(AII)**.
- 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 a trial of inhaled pulmonary vasodilator as a rescue therapy; if no rapid improvement in oxygenation is observed, the patient should be tapered off treatment **(CIII)**.
- There are insufficient data to recommend either for or against the routine use of extracorporeal membrane oxygenation for patients with COVID-19 and refractory hypoxemia **(BIII)**.

Drug Therapy:

- There are insufficient data for the Panel to recommend either for or against any immunomodulatory therapy in patients with severe COVID-19 disease **(AIII)**.
- 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)**.
- The Panel **recommends against** the routine use of systemic corticosteroids for the treatment of mechanically ventilated patients with COVID-19 without ARDS **(BIII)**.
- In mechanically ventilated adults with COVID-19 and ARDS, there are insufficient data to recommend either for or against corticosteroid therapy in the absence of another indication **(CI)**.
- In COVID-19 patients with refractory shock, low-dose corticosteroid therapy is preferred over no corticosteroid therapy **(BII)**.

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

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

General Considerations

(Last updated April 21, 2020)

Co-Morbid Conditions

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

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

Bacterial Superinfection of COVID-19-Associated Pneumonia

Limited information exists about the frequency and microbiology of pulmonary coinfections and superinfections in patients with COVID-19, such as hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP). Some studies from China emphasize the lack of bacterial coinfections in patients with COVID-19, while other studies suggest that these patients experience frequent bacterial complications.[2-7] There is appropriate concern about performing pulmonary diagnostic procedures, such as bronchoscopy or other airway sampling that requires disruption of a closed airway circuit. Thus, while some clinicians do not routinely start empiric broad-spectrum antimicrobial therapy for COVID-19 patients with severe disease, other experienced clinicians routinely use such therapy. For the treatment of shock, however, broad-spectrum empiric antimicrobial therapy is standard of care. Antibiotic stewardship is critical to avoid reflexive or continued courses of antibiotics.

Septic Shock and Cytokine Storm Due to COVID-19

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

COVID-19-Induced Cardiac Dysfunction, Including Myocarditis

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

Renal and Hepatic Dysfunction Due to COVID-19

Although SARS-CoV-2 is primarily a pulmonary pathogen, renal and hepatic dysfunction are consistently described in patients with severe disease.[3] Continuous renal replacement therapy was needed in more than 15% of cases of critical disease in one series.[5]

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

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

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

Other Intensive Care Unit-Related Complications

Patients who are critically ill with COVID-19 are at risk for nosocomial infections and other complications of critical illness care, such as VAP, HAP, catheter-related bloodstream infections, and venous thromboembolism. The focus on COVID-19 should not reduce attention to minimizing conventional ICU complications in order to optimize the likelihood of a successful ICU outcome.

Goals of Care

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

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

References

1. Garg S, Kim L, Whitaker M, et al. Hospitalization Rates and Characteristics of Patients Hospitalized with Laboratory-Confirmed Coronavirus Disease 2019 - COVID-NET, 14 States, March 1-30, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(15):458-464. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32298251.

2. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32167524.

3. Arentz M, Yim E, Klaff L, et al. Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. *JAMA*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32191259.

4. Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in Critically Ill Patients in the Seattle Region - Case Series. *N Engl J Med*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32227758.

5. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32105632.

6. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ*. 2020;368:m1091. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32217556.

7. Du Y, Tu L, Zhu P, et al. Clinical Features of 85 Fatal Cases of COVID-19 from Wuhan: A Retrospective Observational Study. *Am J Respir Crit Care Med*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32242738.

8. Shi S, Qin M, Shen B, et al. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. *JAMA Cardiol*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32211816.

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

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

11. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32031570.

12. White DB, Lo B. A Framework for Rationing Ventilators and Critical Care Beds During the COVID-19 Pandemic. *JAMA*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32219367.

13. Curtis JR, Kross EK, Stapleton RD. The Importance of Addressing Advance Care Planning and Decisions About Do-Not-Resuscitate Orders During Novel Coronavirus 2019 (COVID-19). *JAMA*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32219360.

14. Alhazzani W, Moller MH, Arabi YM, et al. Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19). *Crit Care Med*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32224769.

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.

References

1. Yam LY, Chen RC, Zhong NS. SARS: ventilatory and intensive care. *Respirology*. 2003;8 Suppl:S31-35. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15018131.

2. Twu SJ, Chen TJ, Chen CJ, et al. Control measures for severe acute respiratory syndrome (SARS) in Taiwan. *Emerg Infect Dis*. 2003;9(6):718-720. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12781013.

3. Milton DK, Fabian MP, Cowling BJ, Grantham ML, McDevitt JJ. Influenza virus aerosols in human exhaled breath: particle size, culturability, and effect of surgical masks. *PLoS Pathog*. 2013;9(3):e1003205. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23505369.

4. Qian H, Li Y, Sun H, Nielsen PV, Huang X, Zheng X. Particle removal efficiency of the portable HEPA air cleaner in a simulated hospital ward. *Building Simulation*. 2010;3:215–224. Available at: https://link.springer.com/article/10.1007/s12273-010-0005-4.

5. Offeddu V, Yung CF, Low MSF, Tam CC. Effectiveness of masks and respirators against respiratory infections in healthcare workers: a systematic review and meta-analysis. *Clin Infect Dis*. 2017;65(11):1934-1942. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29140516.

6. World Health Organization. Infection prevention and control during health care when novel coronavirus (nCoV) infection is suspected. 2020. https://www.who.int/publications-detail/infection-prevention-and-control-during-health-care-when-novel-coronavirus-(ncov)-infection-is-suspected-20200125. Accessed May 9, 2020.

7. Centers for Disease Control and Prevention. Interim infection prevention and control recommendations for patients with suspected or confirmed coronavirus disease 2019 (COVID-19) in Healthcare Settings. 2020; https://www.cdc.gov/coronavirus/2019-ncov/infection-control/control-recommendations.html. Accessed April 8, 2020.

8. Smith JD, MacDougall CC, Johnstone J, Copes RA, Schwartz B, Garber GE. Effectiveness of N95 respirators versus surgical masks in protecting health care workers from acute respiratory infection: a systematic review and meta-analysis. *CMAJ*. 2016;188(8):567-574. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26952529.

9. Tran K, Cimon K, Severn M, Pessoa-Silva CL, Conly J. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review. *PLoS One*. 2012;7(4):e35797. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22563403.

10. Lewis SR, Butler AR, Parker J, Cook TM, Schofield-Robinson OJ, Smith AF. Videolaryngoscopy versus direct laryngoscopy for adult patients requiring tracheal intubation: a Cochrane Systematic Review. *Br J Anaesth*. 2017;119(3):369-383. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28969318.

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.

References

1. Chan PK, To WK, Ng KC, et al. Laboratory diagnosis of SARS. *Emerg Infect Dis*. 2004;10(5):825-831. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15200815.

2. Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in different types of clinical specimens. *JAMA*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32159775.

3. Centers for Disease Control and Prevention. Evaluating and testing persons for coronavirus disease 2019 (COVID-19). 2020; https://www.cdc.gov/coronavirus/2019-nCoV/hcp/clinical-criteria.html. Accessed April 8, 2020.

4. Hase R, Kurita T, Muranaka E, Sasazawa H, Mito H, Yano Y. A case of imported COVID-19 diagnosed by PCR-positive lower respiratory specimen but with PCR-negative throat swabs. *Infect Dis (Lond)*. 2020:1-4. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32238024.

5. Tang P, Louie M, Richardson SE, et al. Interpretation of diagnostic laboratory tests for severe acute respiratory syndrome: the Toronto experience. *CMAJ*. 2004;170(1):47-54. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14707219.

6. Memish ZA, Al-Tawfiq JA, Makhdoom HQ, et al. Respiratory tract samples, viral load, and genome fraction yield in patients with Middle East respiratory syndrome. *J Infect Dis*. 2014;210(10):1590-1594. Available at:

https://www.ncbi.nlm.nih.gov/pubmed/24837403.

7. Centers for Disease Control and Prevention. Interim guidelines for collecting, handling, and testing clinical specimens from persons under investigation (PUIs) for Middle East respiratory syndrome coronavirus (MERS-CoV).Version 2.1. 2020. Available at: https://www.cdc.gov/coronavirus/mers/guidelines-clinical-specimens.html. Accessed April 8, 2020.

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.

References

1. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. *Crit Care Med*. 2017;45(3):486-552. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28098591.

2. Bednarczyk JM, Fridfinnson JA, Kumar A, et al. Incorporating dynamic assessment of fluid responsiveness into goal-directed therapy: a systematic review and meta-analysis. *Crit Care Med*. 2017;45(9):1538-1545. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28817481.

3. Bentzer P, Griesdale DE, Boyd J, MacLean K, Sirounis D, Ayas NT. Will this hemodynamically unstable patient respond to a bolus of intravenous fluids? *JAMA*. 2016;316(12):1298-1309. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27673307.

4. Pan J, Peng M, Liao C, Hu X, Wang A, Li X. Relative efficacy and safety of early lactate clearance-guided therapy resuscitation in patients with sepsis: a meta-analysis. *Medicine (Baltimore)*. 2019;98(8):e14453. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30813144.

5. Semler MW, Self WH, Wanderer JP, et al. Balanced crystalloids versus saline in critically ill adults. *N Engl J Med*. 2018;378(9):829-839. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29485925.

6. Brown RM, Wang L, Coston TD, et al. Balanced crystalloids versus saline in sepsis. a secondary analysis of the SMART clinical trial. *Am J Respir Crit Care Med*. 2019;200(12):1487-1495. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31454263.

7. Antequera Martin AM, Barea Mendoza JA, Muriel A, et al. Buffered solutions versus 0.9% saline for resuscitation in critically ill adults and children. *Cochrane Database Syst Rev*. 2019;7:CD012247. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31334842.

8. Lewis SR, Pritchard MW, Evans DJ, et al. Colloids versus crystalloids for fluid resuscitation in critically ill people. *Cochrane Database Syst Rev*. 2018;8:CD000567. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30073665.

9. Delaney AP, Dan A, McCaffrey J, Finfer S. The role of albumin as a resuscitation fluid for patients with sepsis: a systematic review and meta-analysis. *Crit Care Med*. 2011;39(2):386-391. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21248514.

Oxygenation and Ventilation

(Last updated May 12, 2020)

For mechanically ventilated patients, the recommendations below emphasize well-described and documented recommendations from the Surviving Sepsis Campaign (SSC) Guidelines for adult sepsis, pediatric sepsis, and COVID-19, which provide more details about management and the data supporting the recommendations.

Recommendations:

- 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 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)**.

Rationale

Hypoxemia is common in hospitalized patients with COVID-19. Criteria for admission to the hospital, intensive care unit (ICU) admission, and mechanical ventilation differ in various 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.[6,7]

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

In the subgroup of more severely hypoxemic patients with PaO_2/FiO_2 ≤200, HFNC reduced the rate of intubation compared to conventional oxygen therapy or NIPPV (HRs 2.07 and 2.57, respectively). These findings were corroborated in a meta-analysis that showed a lower likelihood of intubation (odds ratio [OR] 0.48; 95% CI, 0.31–0.73) and ICU mortality (OR 0.36; 95% CI, 0.20–0.63) with HFNC than with NIPPV.[9] In situations where the options for respiratory support are limited, reducing the need for intubation may be particularly important.

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[10,11] and patients with acute respiratory distress syndrome (ARDS).[12,13] NIPPV may generate aerosol spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and thus increase nosocomial transmission of the infection.[14,15] It remains uncertain whether HFNC results in less risk of nosocomial SARS-CoV-2 transmission due to aerosol generation.

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 increased hospital mortality (relative risk 1.21; 95% CI, 1.03–1.43).[16]

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

Recommendations:

- For mechanically ventilated adults with COVID-19 and ARDS:
  - The Panel recommends using low tidal volume (Vt) ventilation (Vt 4–8 mL/kg of predicted body weight) over higher tidal volumes (Vt >8 mL/kg) **(AI)**.
  - The Panel recommends targeting plateau pressures of <30 cm H_2O **(AII)**.
  - The Panel recommends using a conservative fluid strategy over a liberal fluid strategy **(BII)**.
  - The Panel **recommends against** the routine use of inhaled nitric oxide **(AI)**.

Rationale

Currently there is no evidence that ventilator management of patients with ARDS due to COVID-19 should differ from 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 optimizing ventilation, the Panel recommends prone ventilation for 12 to 16 hours per day over no prone ventilation **(BII)**.

Rationale

Proning is a recommended strategy in non-COVID-19-related ARDS for improving oxygenation and reducing the heterogeneity of lung ventilation. Proning has been used to treat patients with COVID-19,

although there is currently not enough clinical experience with this strategy to draw conclusions about its effect on long-term outcomes.[18] However, even in centers that are experienced in prone ventilation, proning requires multiple staff members to safely turn the patient and prevent dislodgement of the endotracheal tube, as well as other tubes and catheters. Each staff member should wear the recommended personal protective equipment (PPE). Depending on local resources, especially when PPE may be in short supply, the risk of COVID-19 exposure during the process of proning may outweigh the benefit of proning to the patient.

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 ventilator dyssynchrony, which places the patient at risk for ventilator lung injury, the need for 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. Thus, in some situations the risks of COVID-19 exposure and the use of PPE for each entry may outweigh the benefit of NMBA treatment.

Recommendations:

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

  - The Panel recommends using recruitment maneuvers rather than not using recruitment maneuvers **(CII)**.

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

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

References

1. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32109013.

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

3. Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. *JAMA*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32191259.

4. Alhazzani W, Moller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Crit Care Med*. 2020. Available at: https://pubmed.ncbi.nlm.nih.gov/32224769/.

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

6. Xu XP, Zhang XC, Hu SL, et al. Noninvasive ventilation in acute hypoxemic nonhypercapnic respiratory failure: a systematic review and meta-analysis. *Crit Care Med*. 2017;45(7):e727-e733. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28441237.

7. Zhao H, Wang H, Sun F, Lyu S, An Y. High-flow nasal cannula oxygen therapy is superior to conventional oxygen therapy but not to noninvasive mechanical ventilation on intubation rate: a systematic review and meta-analysis. *Crit Care*. 2017;21(1):184. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28701227.

8. Frat JP, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med*. 2015;372(23):2185-2196. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25981908.

9. Ni YN, Luo J, Yu H, Liu D, Liang BM, Liang ZA. The effect of high-flow nasal cannula in reducing the mortality and the rate of endotracheal intubation when used before mechanical ventilation compared with conventional oxygen therapy and noninvasive positive pressure ventilation. A systematic review and meta-analysis. *Am J Emerg Med*. 2018;36(2):226-233. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28780231.

10. Alraddadi BM, Qushmaq I, Al-Hameed FM, et al. Noninvasive ventilation in critically ill patients with the Middle East respiratory syndrome. *Influenza Other Respir Viruses*. 2019;13(4):382-390. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30884185.

11. Esquinas AM, Egbert Pravinkumar S, Scala R, et al. Noninvasive mechanical ventilation in high-risk pulmonary infections: a clinical review. *Eur Respir Rev*. 2014;23(134):427-438. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25445941.

12. He H, Sun B, Liang L, et al. A multicenter RCT of noninvasive ventilation in pneumonia-induced early mild acute respiratory distress syndrome. *Crit Care*. 2019;23(1):300. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31484582.

13. Antonelli M, Conti G, Moro ML, et al. Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multi-center study. *Intensive Care Med*. 2001;27(11):1718-1728. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11810114.

14. Tran K, Cimon K, Severn M, Pessoa-Silva CL, Conly J. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review. *PLoS One*. 2012;7(4):e35797. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22563403.

15. Yu IT, Xie ZH, Tsoi KK, et al. Why did outbreaks of severe acute respiratory syndrome occur in some hospital wards but not in others? *Clin Infect Dis*. 2007;44(8):1017-1025. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17366443.

16. Chu DK, Kim LH, Young PJ, et al. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. *Lancet*. 2018;391(10131):1693-1705. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29726345.

17. Barrot L, Asfar P, Mauny F, et al. Liberal or conservative oxygen therapy for acute respiratory distress syndrome. *N Engl J Med*. 2020;382(11):999-1008. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32160661.

18. Pan C, Chen L, Lu C, et al. Lung recruitability in SARS-CoV-2 associated acute respiratory distress syndrome: a single-center, observational study. *Am J Respir Crit Care Med*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32200645.

Pharmacologic Interventions

(Last updated April 21, 2020)

Recommendations:

- There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against any immunomodulatory therapy in COVID-19 patients with severe disease **(AIII)**.

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

Rationale

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-CoV 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 and C-reactive protein, but typically not procalcitonin.

There are no data from randomized clinical trials or large observational cohort studies describing the efficacy of tocilizumab among patients with COVID-19. There are anecdotal reports of improved oxygenation in patients with COVID-19, systemic inflammation, and hypoxic respiratory failure.

The primary laboratory abnormalities reported with tocilizumab treatment are elevated levels of liver enzymes that appear to be dose dependent. Neutropenia or thrombocytopenia are uncommon. Additional adverse events, such as risk for serious infections (e.g., tuberculosis, other bacterial pathogens), have been reported only in the context of continuous dosing of tocilizumab.[2-7]

Clinicians have used tocilizumab for desperately ill patients. The results of ongoing trials will enable clinicians to make evidence-based decisions about whether to use this drug and how to best use it.

Recommendations:

- The Panel **recommends against** the routine use of systemic corticosteroids for the treatment of mechanically ventilated patients with COVID-19 without acute respiratory distress syndrome (ARDS) **(BIII)**.

- In mechanically ventilated adults with COVID-19 and ARDS, there are insufficient data to recommend either for or against corticosteroid therapy in the absence of another indication **(CI)**.

Rationale

No randomized clinical trials of corticosteroid use in patients with COVID-19, including those with severe disease, have been performed.

Cytokine elevations have been described in patients with severe COVID-19 pneumonia; thus, clinicians have used corticosteroids to treat severe COVID-19.[8,9] In addition, the anti-inflammatory properties of corticosteroids may help suppress the inflammatory and cytokine-related lung injury that is characteristic

of ARDS.

Prior experience with influenza and other coronaviruses may be relevant. A recent Cochrane analysis of influenza pneumonia demonstrated increased mortality and increased incidence of hospital-acquired pneumonia (HAP) in patients who were administered corticosteroids.[10] The analysis was confounded by study heterogeneity, including different dosage regimens and different durations of therapy for corticosteroid interventions.

For Middle East respiratory syndrome (MERS), severe acute respiratory syndrome (SARS), and influenza, some studies have demonstrated an association between corticosteroid use and delayed viral clearance.[11-13]

Limited data have been published from uncontrolled studies that used varying doses and durations of corticosteroid therapy for COVID-19. A recent retrospective series of patients with COVID-19 and associated ARDS observed, in an unadjusted analysis, a decrease in mortality (hazard ratio 0.38; 95% confidence interval, 0.20–0.72) with methylprednisolone, but there were confounding factors in this analysis.[14]

In the absence of ARDS, the routine use of corticosteroids is not recommended, although patients with COVID-19 may have other indications to receive corticosteroids, including refractory shock or myocarditis.[10,15]

Clinicians have used corticosteroids in severe and critical COVID-19.[14] The results of ongoing trials will enable clinicians to make evidence-based decisions about whether to use this drug and will help define the optimal timing, dose, and duration of corticosteroid therapy in patients with COVID-19, including those with ARDS (a list of these clinical trials is available on *ClinicalTrials.gov*).

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 chest x-ray, leukocytosis, an elevated serum lactate, microbiologic data, or shock.

Gram stain and cultures or testing of respiratory specimens are often not available due to concern about aerosolization of 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.[16] 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.

References

1. Yoshikawa T, Hill T, Li K, Peters CJ, Tseng CT. Severe acute respiratory syndrome (SARS) coronavirus-induced lung epithelial cytokines exacerbate SARS pathogenesis by modulating intrinsic functions of monocyte-derived macrophages and dendritic cells. *J Virol*. 2009;83(7):3039-3048. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19004938.

2. Brunner HI, Ruperto N, Zuber Z, et al. Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomised, double-blind withdrawal trial. *Ann Rheum Dis*. 2015;74(6):1110-1117. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24834925.

3. Genovese MC, van Adelsberg J, Fan C, et al. Two years of sarilumab in patients with rheumatoid arthritis and an inadequate response to MTX: safety, efficacy and radiographic outcomes. *Rheumatology (Oxford)*. 2018;57(8):1423-1431. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29746672.

4. Yokota S, Imagawa T, Mori M, et al. Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. *Lancet*. 2008;371(9617):998-1006. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18358927.

5. Le RQ, Li L, Yuan W, et al. FDA approval summary: tocilizumab for treatment of chimeric antigen receptor T cell-induced severe or life-threatening cytokine release syndrome. *Oncologist*. 2018;23(8):943-947. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29622697.

6. Campbell L, Chen C, Bhagat SS, Parker RA, Ostor AJ. Risk of adverse events including serious infections in rheumatoid arthritis patients treated with tocilizumab: a systematic literature review and meta-analysis of randomized controlled trials. *Rheumatology (Oxford)*. 2011;50(3):552-562. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21078627.

7. Geng Z, Yu Y, Hu S, Dong L, Ye C. Tocilizumab and the risk of respiratory adverse events in patients with rheumatoid arthritis: a systematic review and meta-analysis of randomised controlled trials. *Clin Exp Rheumatol*. 2019;37(2):318-323. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30183597.

8. Gao Y, Li T, Han M, et al. Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. *J Med Virol*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32181911.

9. Conti P, Ronconi G, Caraffa A, et al. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. *J Biol Regul Homeost Agents*. 2020;34(2). Available at: https://www.ncbi.nlm.nih.gov/pubmed/32171193.

10. 10. Alhazzani W, Moller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Intensive Care Med*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32222812.

11. Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid therapy for critically ill patients with Middle East respiratory syndrome. *Am J Respir Crit Care Med*. 2018;197(6):757-767. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29161116.

12. Lee N, Allen Chan KC, Hui DS, et al. Effects of early corticosteroid treatment on plasma SARS-associated coronavirus RNA concentrations in adult patients. *J Clin Virol*. 2004;31(4):304-309. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15494274.

13. Lee N, Chan PK, Hui DS, et al. Viral loads and duration of viral shedding in adult patients hospitalized with influenza. *J Infect Dis*. 2009;200(4):492-500. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19591575.

14. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. 2020. Available at:

https://www.ncbi.nlm.nih.gov/pubmed/32167524.

15. Hu H, Ma F, Wei X, Fang Y. Coronavirus fulminant myocarditis saved with glucocorticoid and human immunoglobulin. *Eur Heart J*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32176300.

16. Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical practice guidelines by the Infectious Diseases Society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza. *Clin Infect Dis*. 2019;68(6):e1-e47. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30566567.

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*.

References

1. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet*. 2009;374(9698):1351-1363. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19762075.

2. Pham T, Combes A, Roze H, et al. Extracorporeal membrane oxygenation for pandemic influenza A(H1N1)-induced acute respiratory distress sy ndrome: a cohort study and propensity-matched analysis. *Am J Respir Crit Care Med*. 2013;187(3):276-285. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23155145.

3. Harrington D, Drazen JM. Learning from a trial stopped by a data and safety monitoring board. *N Engl J Med*. 2018;378(21):2031-2032. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29791830.

4. Munshi L, Walkey A, Goligher E, Pham T, Uleryk EM, Fan E. Venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: a systematic review and meta-analysis. *Lancet Respir Med*. 2019;7(2):163-172. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30642776.

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

(Last updated May 12, 2020)

Summary Recommendations
There are no Food and Drug Administration (FDA)-approved drugs for the treatment of COVID-19. Although reports have appeared in the medical literature and the lay press claiming successful treatment of patients with COVID-19 with a variety of agents, definitive clinical trial data are needed to identify safe and effective treatments for this disease. Recommended clinical management of patients with COVID-19 includes infection prevention and control measures and supportive care, including supplemental oxygen and mechanical ventilatory support when indicated. As in the management of any disease, treatment decisions ultimately reside with the patient and their health care provider.

Antivirals:

- On the basis of preliminary clinical trial data, the COVID-19 Treatment Guidelines Panel (the Panel) recommends the investigational antiviral agent **remdesivir** for the treatment of COVID-19 in hospitalized patients with severe disease defined as SpO_2 ≤94% on ambient air (at sea level), requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation **(BI)**.
  - Remdesivir is not approved by the FDA. It is available through an FDA emergency use authorization, in clinical trials, or through an emergency access program for children and pregnant patients.
- The Panel **does not recommend remdesivir** for the treatment of mild or moderate COVID-19 outside of a clinical trial **(AIII)**.
- There are insufficient clinical data to recommend either for or against using **chloroquine** or **hydroxychloroquine** for the treatment of COVID-19 **(AIII)**.
- The Panel **recommends against** using high-dose chloroquine (600 mg twice daily for 10 days) for the treatment of COVID-19 **(AI)**.
- Except in the context of a clinical trial, the Panel **recommends against** the use of the following drugs for the treatment of COVID-19:
  - 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 negative clinical trial data.

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

For more information on the antiviral agents that are under evaluation for COVID-19, see Tables 2a and 2b.

Remdesivir

(Last updated May 12, 2020)

Recommendations:

- On the basis of preliminary clinical trial data (described below), the COVID-19 Treatment Guidelines Panel (the Panel) recommends the investigational antiviral agent **remdesivir** for the treatment of COVID-19 in hospitalized patients with severe disease (defined as having SpO_2 ≤94% on ambient air [at sea level], requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation [ECMO]) **(BI)**.
  - Remdesivir is not approved by the Food and Drug Administration (FDA); however, it is available through an FDA emergency use authorization (EUA) for the treatment of hospitalized adults and children with COVID-19 and is currently being investigated in clinical trials. Remdesivir is also available through an emergency access program for children (<18 years of age) and pregnant patients.
  - Additional data on the use of remdesivir for patients with COVID-19, including analyses of important patient subgroups, are expected soon and may further inform the Panel's recommendation.
- The Panel **does not recommend** using **remdesivir** for the treatment of mild or moderate COVID-19 outside of a clinical trial **(AIII)**.

Rationale for Recommendations:

Preliminary data from a multi-national, randomized, placebo-controlled trial (Adaptive COVID-19 Treatment Trial [ACTT]) of hospitalized patients with COVID-19 showed that patients who were randomized to receive remdesivir had a shorter time to clinical recovery than those who received placebo. There is not enough clinical trial data to assess the role of remdesivir for patients with mild to moderate COVID-19.

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

Remdesivir is an intravenous investigational nucleotide prodrug of an adenosine analog. It has demonstrated *in vitro* activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),[1] and *in vitro* and *in vivo* activity (based on animal studies) against SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV).[2-4] Remdesivir binds to the viral RNA-dependent RNA polymerase, inhibiting viral replication through premature termination of RNA transcription.

Preclinical studies show that remdesivir improves disease outcomes and reduces levels of SARS-CoV in mice.[2] When given as prophylaxis or therapy, remdesivir also reduces MERS-CoV levels and lung injury in mice. In a rhesus macaque model of MERS-CoV infection, prophylactic remdesivir prevented MERS-CoV clinical disease.[4] When given to rhesus macaques 12 hours after inoculation with MERS-CoV, remdesivir reduced viral replication and the severity of lung disease in treated animals compared to control animals. In a rhesus macaque model of SARS-CoV-2 infection, remdesivir treatment was started soon after inoculation in six of 12 monkeys. The remdesivir-treated animals had lower lung virus levels and less lung damage than the control animals.[5]

Clinical Data to Date

Multinational Randomized Controlled Trial of Remdesivir Versus Placebo in Hospitalized Patients

These data have not been peer reviewed.

ACTT is a National Institutes of Health (NIH)-sponsored international, randomized, double-blind trial of remdesivir versus placebo (1:1 randomization ratio) in hospitalized adult patients (aged ≥18 years) with laboratory confirmed COVID-19 who have at least one of the following clinical manifestations: pulmonary infiltrates by radiographic imaging, SpO_2 ≤94% on ambient air, require supplemental oxygen or mechanical ventilation. The study excluded individuals who had an alanine transaminase or aspartate transaminase level >5 times the upper limit of normal, an estimated glomerular filtration rate (eGFR) <30 ml/min, or who were pregnant or breastfeeding. The primary study endpoint was time to recovery.

Preliminary study data were released on April 29, 2020, after an interim review by the study's independent data safety monitoring board (DSMB). The study enrolled 1,063 participants. Participants who received remdesivir had a 31% faster time to recovery than those who received placebo (median recovery time of 11 days vs. 15 days, respectively; HR, 1.31; 95% CI, 1.12 to 1.54, $P < 0.001$).[6] The preliminary results also showed a mortality rate of 8.0% and 11.6% for the remdesivir and placebo groups, respectively ($P = 0.059$). The study data have not been peer reviewed. Additional results, including analyses of important patient subgroups, are expected soon.[7]

Limitations:

Only the preliminary analysis is available after the DSMB review. A full report of the study results is still forthcoming.

Interpretation:

This trial is the first randomized, double-blinded, fully powered study to demonstrate the clinical benefit of a pharmacological treatment for COVID-19.

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

Study Design:

Multicenter, double-blind, randomized, placebo-controlled trial in patients with severe COVID-19 in China.[8] Patients were randomized 2:1 to intravenous remdesivir or normal saline placebo for 10 days. Concomitant use of lopinavir/ritonavir, corticosteroids, and interferons were allowed. The primary study endpoint was time to clinical improvement, defined as improvement on an ordinal scale or discharged alive from the hospital, whichever came first. The planned sample size was 453 patients.

Participant Population:

Hospitalized adults with laboratory confirmed COVID-19, symptom onset to randomization <12 days, O_2 saturation ≤ 94% on room air, or PaO_2/FiO_2; <300 mmHg, with radiographically confirmed pneumonia.

Results:

237 hospitalized patients were enrolled and randomized to treatment (158 patients to remdesivir vs. 79 patients to placebo) from February 6, 2020, to March 12, 2020. The study was stopped before the target enrollment was reached due to control of the COVID-19 outbreak in China.

- The median age of the participants was 65 years; 56% of the participants in the remdesivir arm and 65% of the participants in the placebo arm were male.
- There were more patients with hypertension, diabetes, or coronary artery disease in the remdesivir arm than in the placebo arm.

- At Day 1, 83% of the participants required supplemental oxygen by nasal cannula or mask; only one participant required mechanical ventilation or ECMO.
- The median time from symptom onset to randomization was 9 days in the remdesivir group and 10 days in the placebo group.
- 65% of the participants in the remdesivir group and 68% of the participants in the placebo group received corticosteroids.
- In both arms, 28% to 29% of the participants 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).
- Though not statistically significant, for patients who started study drug within 10 days of symptom onset, faster time to clinical improvement was seen in the remdesivir arm than in the placebo arm (median 18.0 days vs. 23.0 days, respectively; HR 1.52, 95% CI, 0.95–2.43]).
- The 28-day mortality rate was similar for the two study arms (14% and 13% of participants in the remdesivir arm and placebo arm, respectively).
- There was no difference between the groups in SARS-CoV-2 viral load at baseline, and the rate of decline over time was similar between the two groups.
- The number of participants who had adverse events was similar in the two groups (66% and 64% of participants in the remdesivir and placebo groups, respectively).
- More participants in the remdesivir arm than in the placebo arm discontinued therapy due to adverse events (12% vs. 5% of participants in the remdesivir and placebo groups, respectively).

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

Interpretation:
There was no difference in time to clinical improvement, 28-day mortality, or rate of viral clearance between the remdesivir-treated patients and placebo-treated patients. The study was terminated early, which resulted in a sample size that was too small to detect differences in clinical outcomes.

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 use of remdesivir led to the improvement.[9]

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

Monitoring, Adverse Effects, and Drug-Drug Interactions:

Remdesivir can cause gastrointestinal symptoms (e.g., nausea, vomiting), elevated transaminase levels, and prothrombin time elevation (without change in international normalized ratio). *In vitro*, remdesivir is a CYP450 (CYP) 3A4, CYP2C8, and CYP2D6 substrate. Coadministration of remdesivir with inhibitors of these enzymes is not expected to have a significant impact on remdesivir concentrations. Remdesivir concentration may be affected by strong CYP inducers, but the interaction is not expected to be clinically significant.[10]

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

Considerations in Pregnancy:

- Use remdesivir in pregnant patients only if the potential benefit justifies the potential risk for the mother and the fetus.[6]

- The safety and effectiveness of remdesivir for COVID-19 treatment have not been evaluated in pregnant patients. Remdesivir should not be withheld from pregnant patients if otherwise indicated.

- Remdesivir is available through the FDA EUA for adults and children and through a compassionate access program for pregnant women with COVID-19.

- In a randomized controlled Ebola treatment trial of therapies including remdesivir, among 98 females who received remdesivir, six had a positive pregnancy test; the obstetric and neonatal outcomes were not reported in the study.[11]

Considerations in Children:

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

- Remdesivir is available through an FDA EUA and through a compassionate access program for patients aged <18 years with COVID-19.

- In the same randomized, controlled trial for the treatment of Ebola virus infection, 41 pediatric patients aged <7 days to <18 years received remdesivir.[11] The safety and clinical outcomes in children were not reported separately in the published results for the trial.

References

1. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) *in vitro*. *Cell Res*. 2020;30(3):269-271. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32020029.

2. Sheahan TP, Sims AC, Graham RL, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. *Sci Transl Med*. 2017;9(396). Available at: https://www.ncbi.nlm.nih.gov/pubmed/28659436.

3. Sheahan TP, Sims AC, Leist SR, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat Commun*. 2020;11(1):222. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31924756.

4. de Wit E, Feldmann F, Cronin J, et al. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. *Proc Natl Acad Sci U S A*. 2020;117(12):6771-6776. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32054787.

5. Williamson BN, Feldmann F, Benjamin Schwarz B, et al. Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. *bioRxiv*. 2020;[Preprint]. Available at: https://www.biorxiv.org/content/10.1101/2020.04.15.043166v2.full.pdf.

6. Food and Drug Administration. Fact sheet for health care providers emergency use authorization (EUA) of remdesivir (GS-5734™). 2020. Available at: https://www.fda.gov/media/137566/download. Accessed: May 8, 2020.

7. NIH clinical trial shows Remdesivir accelerates recovery from advanced COVID-19. April 29, 2020;[Press release].

8. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *The Lancet*. 2020. Available at: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31022-9/fulltext#seccestitle10.

9. Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe COVID-19. *N Engl J Med*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32275812.

10. Remdesivir (GS-5734) [investigator's brochure]. Edition 5. Gilead Sciences. February 21, 2020.

11. Mulangu S, Dodd LE, Davey RT, Jr., et al. A Randomized, controlled trial of ebola virus disease therapeutics. *N Engl J Med*. 2019;381(24):2293-2303. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31774950.

Chloroquine or Hydroxychloroquine

(Last updated May 12, 2020)

Overall Recommendation:

- There are insufficient clinical data to recommend either for or against using **chloroquine** or **hydroxychloroquine** for the treatment of COVID-19 **(AIII)**.
- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** using **high-dose chloroquine** (600 mg twice daily for 10 days) for the treatment of COVID-19 **(AI)**.

Rationale for Recommendation

Chloroquine and hydroxychloroquine have been used in small randomized trials and in some case series and clinical trials with conflicting study reports (as described below). Both drugs are available through the Strategic National Stockpile for hospitalized adults and adolescents weighing ≥50 kg who cannot access these drugs through a clinical trial.[1]

Reports have documented serious dysrhythmias in patients with COVID-19 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 the setting 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 versus low-dose chloroquine in patients with COVID-19; in addition, all of the 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.

Background

Chloroquine is an antimalarial drug 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 (RA). 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 for COVID-19:

- Both chloroquine and hydroxychloroquine increase the endosomal pH, inhibiting fusion of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the host cell membranes.[3]
- Chloroquine inhibits glycosylation of the cellular angiotensin-converting enzyme 2 receptor, which may interfere with binding of SARS-CoV to the cell receptor.[4]
- *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.[5]
- Several studies have demonstrated *in vitro* activity of chloroquine against SARS-CoV.[4,6]
- Both chloroquine and hydroxychloroquine have immunomodulatory effects.

Clinical Data for COVID-19

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

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, heart rate >125, oxygen saturation <90%, and/or shock).[7] All patients received ceftriaxone plus azithromycin; 89.6% of the 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 in 16 of 41 patients [39%] vs. in 6 of 40 patients [15%]; P = 0.03). This difference was no longer significant when controlled by age (OR 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 (11.1%) arm. Among those with confirmed COVID-19, QTcF >500 ms was also more frequent 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 concern for increased mortality with high-dose chloroquine (600 mg twice daily) 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.[8] Patients with a history of heart disease (chronic disease and 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 determined by evaluation of study drug-related AEs.

Results:

- Ten 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, there was no significant clinical benefit seen with chloroquine compared to lopinavir/ritonavir in the treatment of COVID-19.

Hydroxychloroquine

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 hospitalized at the United States Veterans Health Administration medical centers between March 9, 2020, and April 11, 2020, with confirmed COVID-19.[9] 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 hazard ratio [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 of hydroxychloroquine and azithromycin are 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.

- Use of other antiviral or immune modulatory agents was not reported.

- The reason for the high mortality in patients who did not receive mechanical ventilation is not clear, especially as most of these patients appear to have had mild/moderate disease on admission.

Interpretation

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

Randomized, Controlled Trial of Hydroxychloroquine Versus Standard of Care

This study has not been peer reviewed.

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 one patient with severe disease) versus standard of care (SOC).[10]

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), markers of inflammation (including C-reactive protein [CRP]), and chest X-ray within 28 days. Secondary outcomes for severe cases included all-cause mortality, clinical status, days of mechanical ventilation, extracorporeal membrane oxygenation (ECMO), supplemental oxygenation, and hospital stay.

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 negative PCR conversion rate by age, body mass index, co-morbid conditions, days between symptom onset and randomization, or other conditions analyzed.
- There was no difference in the rate of symptom alleviation between the groups in the intention-to-treat analysis.
- There was more rapid normalization of CRP and lymphocytopenia in the hydroxychloroquine group.
- Adverse effects occurred in 30% of the participants in the hydroxychloroquine arm (most commonly diarrhea) versus in 8.8% of the participants in the SOC arm.

Limitations:
- The definition of SOC and the use of concomitant medications (two patients received azithromycin) were not clearly stated.
- 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 or clinical trials for the treatment of COVID-19.
- The authors note that hydroxychloroquine was associated with increased alleviation of symptoms (HR, 8.83; 95% CI, 1.09–71.3), but this was only in a post-hoc subgroup analysis that excluded patients on other antivirals.

Interpretation

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

Observational Cohort of Hydroxychloroquine Versus No Hydroxychloroquine

This study has not been peer reviewed.

This observational, retrospective cohort study analyzed data for adult patients hospitalized for COVID-19 pneumonia at four French tertiary care centers over a 2-week period (March 17–31, 2020).[11] Patients were eligible if they required oxygen by mask or nasal cannula. Patients were excluded if they were immediately admitted to the intensive care unit (ICU) or admitted with acute respiratory distress syndrome (ARDS) (requiring non-invasive ventilation or mechanical ventilation). The treatment arms compared were initiation of hydroxychloroquine at a daily dose of 600 mg within 48 hours of admission and the absence of hydroxychloroquine during the same period. The primary outcome was a composite of transfer to the ICU within 7 days of enrollment and/or death from any cause. An inverse probability of treatment weighting approach was used to "emulate" randomization.

Results:
- 181 patients were eligible for the analysis; 84 participants received hydroxychloroquine and 97 participants did not.
- 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, 20% of the patients received concomitant azithromycin and 76% of the patients received amoxicillin/clavulanic acid.
- In the inverse probability of treatment weighting analysis there was no difference in the

composite outcome between the hydroxychloroquine group (20.5% of participants) and the non-hydroxychloroquine group (22.1% of participants). Similarly, there was no difference between the groups in the secondary outcomes of all-cause mortality and development of ARDS.

- Among the 84 patients receiving hydroxychloroquine, eight patients (9.5%) experienced electrocardiogram (ECG) changes requiring treatment discontinuation at a median of 4 days from the start of dosing, including seven patients with a QTc that prolonged >60 ms and one patient with new onset, first-degree atrioventricular (AV) block.

Limitations:

- This was a retrospective, non-randomized study.
- The number of patients with QTc prolongation who received hydroxychloroquine only versus those who received hydroxychloroquine plus azithromycin was not reported.

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.

Randomized Controlled Trial of Hydroxychloroquine plus Standard Treatment Versus Standard Treatment Alone

This study has not been peer reviewed.

In a randomized controlled trial in China, 62 hospitalized patients with mild (SpO_2 ratio >93% or PaO_2/FIO_2 ratio >300 mm Hg) CT-confirmed COVID-19 pneumonia were randomized to hydroxychloroquine 200 mg twice daily for 5 days plus standard treatment or to standard treatment only.[12] Standard treatment included oxygen therapy, antiviral and antibacterial therapy, and immunoglobin, with or without corticosteroids.

Results:

- Compared to the control patients, the hydroxychloroquine-treated patients had a 1 day-shorter mean duration of fever (2.2 days vs. 3.2 days) and cough (2.0 days vs. 3.1 days).
- Of the control patients, 13% experienced progression of illness; none of the hydroxychloroquine-treated patients experienced progression of illness.
- 80.6% of the hydroxychloroquine-treated patients and 54.8% of the control patients experienced either moderate or significant improvement in chest CT scan.
- Adverse events (one rash, one headache) occurred among two (6.4%) of the hydroxychloroquine-treated patients; none of the control patients experienced an adverse event.

Limitations:

- The trial had a small sample size and short follow-up.
- The standard treatment is complex and not well defined.
- The presence and distribution of associated co-morbidities (e.g., hypertension, diabetes, lung disease) was not reported.
- There was no indication that radiologists were blinded to the treatment status of the patients, which could have biased determination of the chest CT outcome.

Interpretation

The methodological limitations of this study preclude determination of efficacy for hydroxychloroquine.

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., who refused treatment, did not meet eligibility criteria, or were from a different clinic).[13]

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 (70%) hydroxychloroquine-treated patients and 2 of 16 (12.5%) controls.
- Among the hydroxychloroquine patients, 8 of 14 (57.1%) patients who received only hydroxychloroquine and 6 of 6 (100%) patients who received hydroxychloroquine and azithromycin had negative NP PCRs by Day 6.
- Clinical outcomes for all patients were not reported.

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] and fluoroquinolone antibiotics)[14] should be used only if necessary. Consider using doxycycline rather than azithromycin as empiric therapy for atypical pneumonia.

- Baseline and follow-up ECG are recommended when there are potential drug interactions with concomitant medications (e.g., azithromycin) or underlying cardiac diseases.[15]

- The risk-benefit ratio should be closely assessed for patients with cardiac disease, history of ventricular arrhythmia, bradycardia (<50 beats per minute), or uncorrected hypokalemia and/or hypomagnesemia.

- *Other Adverse Effects:*

  - Hypoglycemia, rash, and nausea (daily divided doses may reduce nausea).

  - Retinopathy, bone marrow suppression with long-term use, but 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 initiation of 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 are also P-glycoprotein (P-gp) inhibitors. Use caution when co-administering the drugs with concomitant medications metabolized by CYP2D6 (e.g., certain antipsychotics, beta-blockers, selective serotonin reuptake inhibitors, and methadone) or transported by P-gp (e.g., certain direct-acting oral anticoagulants or digoxin).[16]

Considerations in Pregnancy:

- Anti-rheumatic 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.

- Dosing/pharmacokinetics/pharmacodynamics: No dosing changes in 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 RA and is available commercially. Hydroxychloroquine is not approved for the treatment of COVID-19.

- FDA issued an emergency use authorization (EUA) for the use of chloroquine and hydroxychloroquine donated to the Strategic National Stockpile. The EUA authorizes the use of these donated drugs for the treatment of hospitalized adolescent and adult patients with COVID-19 who weigh ≥50 kg and for whom a clinical trial is not available, or participation is not feasible.

References

1. Food and Drug Administration. Emergency Use Authorization - COVID-19 Therapeutics. 2020. Available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/

emergency-use-authorization#covidtherapeutics. Accessed: April 8, 2020.

2. Food and Drug Administration. FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems. 2020. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or. Accessed: May 8, 2020.

3. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*. 2020;30(3):269-271. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32020029.

4. Vincent MJ, Bergeron E, Benjannet S, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. *Virol J*. 2005;2:69. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16115318.

5. Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov*. 2020;6:16. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32194981.

6. Keyaerts E, Vijgen L, Maes P, Neyts J, Van Ranst M. In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. *Biochem Biophys Res Commun*. 2004;323(1):264-268. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15351731.

7. Borba MGS, Val FFA, Sampaio VS, et al. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial. *JAMA Netw Open*. 2020;3(4):e208857. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32339248.

8. Huang M, Tang T, Pang P, et al. Treating COVID-19 with chloroquine. *J Mol Cell Biol*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32236562.

9. Magagnoli J, Narendran S, Pereira F, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. *medRxiv*. 2020. [Preprint]. Available at: https://www.medrxiv.org/content/10.1101/2020.04.16.20065920v2.

10. Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with COVID-19: an open-label, randomized, controlled trial. *medRxiv*. 2020. [Preprint]. Available at: https://www.medrxiv.org/content/10.1101/2020.04.10.20060558v1.

11. Mahevas M, Tran V, Roumier M, et al. No evidence of clinical efficacy of hydroxychloroquine in patients hospitalized for COVID-19 infection with oxygen requirement: results of a study using routinely collected data to emulate a target trial. *medRxiv*. 2020. [Preprint]. Available at: https://www.medrxiv.org/content/10.1101/2020.04.10.20060699v1.

12. Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. *medRxiv*. 2020. [Preprint]. Available at: https://www.medrxiv.org/content/10.1101/2020.03.22.20040758v2.

13. Gautret P, Lagier J, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *International Journal of Antimicrobial Agents*. 2020. [In press]. Available at: https://www.sciencedirect.com/science/article/pii/S0924857920300996.

14. CredibleMeds. Combined list of drugs that prolong QT and/or cause Torsades de Pointes (TDP). 2020. Available at: https://crediblemeds.org/pdftemp/pdf/CombinedList.pdf

15. American College of Cardiology. Ventricular arrhythmia risk due to hydroxychloroquine-azithromycin treatment for COVID-19. 2020. Available at: https://www.acc.org/latest-in-cardiology/articles/2020/03/27/14/00/ventricular-arrhythmia-risk-due-to-hydroxychloroquine-azithromycin-treatment-for-covid-19. Accessed April 8, 2020.

16. University of Liverpool. COVID-19 drug interactions. 2020. Available at: https://www.covid19-druginteractions.org/. Accessed: May 11, 2020.

Hydroxychloroquine plus Azithromycin

(Last updated May 12, 2020)

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

Recommendation:

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

Rationale for Recommendation

Chloroquine and hydroxychloroquine for COVID-19 have been used in small randomized trials and in some case series with conflicting study reports (as described above). The combination of hydroxychloroquine and azithromycin is associated with QTc prolongation in patients with COVID-19. Given the long half-lives of both azithromycin (up to 72 hours) and hydroxychloroquine (up to 40 days), caution is warranted even when the two drugs are used sequentially instead of concomitantly.[1]

Clinical Data in COVID-19

Case Series of Hydroxychloroquine Plus Azithromycin

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

Clinical Results:

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

Laboratory Results:

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

Limitations:

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

Interpretation:

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

study to inform recommendations.

Small Prospective Case Series of Hydroxychloroquine Plus Azithromycin

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

Results:

- Eight of the 11 patients had significant co-morbid conditions: obesity (2), solid cancer (3), hematological cancer (2), and HIV-infection (1).

- Ten of 11 patients were receiving supplemental oxygen upon treatment initiation.

- All patients were treated with hydroxychloroquine 600 mg once daily for 10 days and azithromycin 500 mg once daily for 1 day followed by 250 mg once daily for 4 days.

- Within 5 days, the condition of three patients worsened, including one patient who died and two patients who were transferred to the ICU.

- Adverse events: Hydroxychloroquine was discontinued in one patient due to QTc prolongation.

- Qualitative NP PCR remained positive at Days 5 and 6 after treatment initiation in 8 of 10 patients.

Limitations:

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

Interpretation:

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

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

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

Results:

- 84 patients, 74% male, mean age 63 ± 15 years, 65% had hypertension, baseline serum creatinine 1.4 mg/dL, 13% required vasopressors, 11% had coronary artery disease.

- Among all the patients, 11% received neuropsychiatric drugs that may prolong QTc interval and 8% received other concomitant drugs (levofloxacin, lopinavir/ritonavir, or tacrolimus) that may prolong QTc.

- Four patients died, without arrhythmia.

- The mean baseline QTc was 435 ± 24 ms; the mean maximum QTc was 463 ± 32 ms.

- The mean time to maximum QTc was 3.6 ± 1.6 days; ECG follow-up was done for a mean of 4.3 days.

- 9 patients (11%) developed QTc >500 ms; the QTc increased by 40 to 60 ms and >60 ms in 18% and 12% of patients, respectively.

Limitations:

- Case series, descriptive

Interpretation:

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

and that use of the combination warrants careful monitoring.

Clinical Trials

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

References

1. Institute for Safe Medication Practices. Medication Safety Alert! April 9, 2020. 2020. Available at: https://ismp.org/acute-care/special-edition-medication-safety-alert-april-9-2020/covid-19. Accessed: April 28, 2020.

2. Gautret P, Lagier JC, Parola P, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study. *Travel Med Infect Dis*. 2020:101663. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32289548.

3. Molina JM, Delaugerre C, Le Goff J, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. *Médecine et Maladies Infectieuses*. 2020;[In press]. Available at: https://www.sciencedirect.com/science/article/pii/S0399077X20300858?via%3Dihub#.

4. Chorin E, Dai M, Shulman E, et al. The QT interval in patients with COVID-19 treated with hydroxychloroquine and azithromycin. *Nature Medicine*. 2020. Available at: https://doi.org/10.1038/s41591-020-0888-2.

Lopinavir/Ritonavir and Other HIV Protease Inhibitors

(Last updated May 12, 2020)

Recommendation:

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

Rationale for Recommendation

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

Lopinavir/Ritonavir

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

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

Clinical Data in COVID-19

Randomized Controlled Trial of Lopinavir/Ritonavir Versus Standard of Care

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

Results:

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

Limitations:

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

Interpretation

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

Lopinavir/Ritonavir Versus Arbidol Versus Standard of Care

This study has not been peer reviewed.

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

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

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

Limitations:

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

Interpretation

The small sample size of this trial limits its usefulness.

Lopinavir/Ritonavir Versus Chloroquine

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

Clinical Trials:

None in the United States

Monitoring, Adverse Effects, and Drug-Drug Interactions

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

Considerations in Pregnancy:

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

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

Considerations in Children:

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

Darunavir/Cobicistat or Darunavir/Ritonavir

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

- Inhibition of the 3CLpro enzyme of SARS-CoV-2 and possibly also inhibition of the PLpro enzyme.
- In an *in vitro* study, darunavir did not show activity against SARS-CoV-2.
- 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.[9]

Clinical Trials:

None in the United States

Other HIV Protease Inhibitors, Including Atazanavir

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

References

1. Zumla A, Chan JF, Azhar EI, Hui DS, Yuen KY. Coronaviruses—drug discovery and therapeutic options. *Nat Rev Drug Discov*. 2016;15(5):327-347. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26868298.

2. Tahir ul Qamar M, Alqahtani SM, Alamri MA, Chen L. Structural basis of SARS-CoV-2 3CLpro and anti-COVID-19 drug discovery from medicinal plants. *Journal of Pharmaceutical Analysis*. 2020. [In press]. Available at: https://www.sciencedirect.com/science/article/pii/S2095177920301271.

3. Liu X, Wang XJ. Potential inhibitors against 2019-nCoV coronavirus M protease from clinically approved medicines. *J Genet Genomics*. 2020;47(2):119-121. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32173287.

4. Chen F, Chan KH, Jiang Y, et al. In vitro susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. *J Clin Virol*. 2004;31(1):69-75. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15288617.

5. Chu CM, Cheng VC, Hung IF, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax*. 2004;59(3):252-256. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14985565.

6. Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19. *N Engl J Med*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32187464.

7. Li Y, Xie Z, Lin W, et al. An exploratory randomized, controlled study on the efficacy and safety of lopinavir/ritonavir or arbidol treating adult patients hospitalized with mild/moderate COVID-19 (ELACOI). *medRxiv*. 2020. [Preprint]. Available at: https://www.medrxiv.org/content/10.1101/2020.03.19.20038984v1.

8. Huang M, Tang T, Pang P, et al. Treating COVID-19 with chloroquine. *J Mol Cell Biol*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32236562.

9. Johnson & Johnson. Lack of evidence to support use of darunavir-based treatments for SARS-CoV-2. 2020. Available at: https://www.jnj.com/lack-of-evidence-to-support-darunavir-based-hiv-treatments-for-coronavirus. Accessed May 11, 2020.

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

(Last updated May 12, 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	Preclinical Data/Mechanism of Action	Clinical Data to Date (Find clinical trials on *ClinicalTrials.gov*)
Azithromycin **Note:** Studies on COVID-19 use AZM with HCQ.	• Mycobacterial (nontuberculous) infection • STIs and various bacterial infections[1]	**Proposed Antiviral Effects:** • Induction of IFN-stimulated genes, attenuating viral replication[2] **Immunomodulatory Effect:** • Enhanced neutrophil activation[3] **Anti-Inflammatory Effects:** • Attenuation of inflammatory cytokines (IL-6 and IL-8) in epithelial cells and inhibition of fibroblast growth factor in airway smooth muscle cells[2]	• AZM is studied for treatment of COVID-19 only in combination with HCQ. • Please see the description of study results in the Hydroxychloroquine plus Azithromycin section below and in Therapeutic Options for COVID-19 Currently Under Investigation.

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

Chloroquine	• Malaria
	• Extra-intestinal amebiasis
		• *In vitro* antiviral activity by increasing the pH of intracellular vacuoles and altering protein degradation pathways, thereby interfering with the virus/cell fusion and glycosylation of cellular receptors[4,5]
		• Inhibits glycosylation of the cellular ACE2 receptor, which may interfere with the binding of the virus to the cell receptor[6]
		• Immunomodulatory effects may lead to a reduction in pro-inflammatory cytokines[5]
			High-Dose vs. Low-Dose CQ[7]
			
			• A randomized, double-blind, Phase 2b study compared two different CQ regimens, CQ 600 mg twice daily for 10 days (high dose) versus CQ 450 mg twice daily for 1 day followed by 450 mg for 4 days (low dose), in hospitalized adults with suspected severe COVID-19 (respiratory rate >24, heart rate >125, 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 into the study.
			
			• *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 in 16 of 41 patients [39%] 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 among patients in the high-dose arm (18.9% of patients) than in the low-dose arm (11.1% of patients). Among those with confirmed COVID-19, QTcF >500 ms was also more frequent in the high-dose arm (24.1% of patients) than in the low-dose arm (3.6% of patients).
			  • Two patients in the high-dose arm experienced ventricular tachycardia before death.
			
			• *Limitations:* More older patients and more patients with history of heart disease were randomized to the high-dose arm than to the low-dose arm.
			
			• *Interpretation:* Despite the small number of patients enrolled, this study raises concern for increased mortality with high-dose CQ (600 mg twice daily) 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 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 history of arrhythmia), or kidney, liver, or hematologic diseases were excluded from participation. Primary study outcome was SARS-CoV-2 PCR negativity 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 determined by evaluation of study drug-related AEs.

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

Chloroquine, continued			• *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 on CQ vs. 6.5 days on LPV/r, P < 0.001).
			  • Though not statistically significant, patients in the chloroquine arm were younger (median age 41.5 years vs. 53.0 years for CQ and LPV/r arms, respectively; *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 negative SARS-CoV-2 PCR. At Day 14, the percentages for the CQ-treated patients and the LPV/r-treated patients were 100% and 91.2%, respectively.
			  • At Day 10, 20% of the CQ-treated patients and 8.3% of the LPV/r-treated patients had CT scan improvement. At Day 14, the percentages for the CQ-treated patients and the LPV/r-treated patients were 100% and 75%, respectively.
			  • At Day 14, 100% of the CQ-treated patients and 50% of the LPV/r-treated patients were discharged from the hospital.
			  • The risk ratios of these outcome data cross 1, and the results were not statistically significant.
			  • Both drugs were generally well-tolerated.
			• *Limitations:*
			  • The trial sample size was very small, and the participants were fairly young.
			  • The CQ-treated patients were younger and had fewer symptoms prior to treatment initiation, which are variables that could have affected the study protocol-defined outcomes.
			  • Patients with chronic comorbidities and critically ill patients were excluded from the study.
			• *Interpretation:* No significant benefit of CQ, but the study was too small to draw conclusions.

Hydroxychloroquine	• Lupus erythematosus • Malaria • Rheumatoid arthritis[9]	• *In vitro* antiviral activity by increasing the pH of intracellular vacuoles and altering protein degradation pathways, thereby interfering with the virus/cell fusion and glycosylation of cellular receptors[4,5] • Immunomodulatory effects may lead to a reduction in pro-inflammatory cytokines.[5]	**Retrospective Observational Cohort from the United States Veterans Health Administration** (*This study has not been peer reviewed*.)[10] • An observational, retrospective cohort study analyzed data from patients hospitalized at the United States Veterans Health Administration medical centers between March 9, 2020, and April 11, 2020, with confirmed COVID-19. Patients were categorized as having received either HCQ, HCQ plus AZM, or no HCQ. Doses and duration of use of HCQ or AZM 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, comorbid, 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.

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

Hydroxychloroquine, continued	• Lupus erythematosus
	• Malaria
	• Rheumatoid arthritis[9]
		• *In vitro* antiviral activity by increasing the pH of intracellular vacuoles and altering protein degradation pathways, thereby interfering with the virus/cell fusion and glycosylation of cellular receptors[4,5]
		• Immunomodulatory effects may lead to a reduction in pro-inflammatory cytokines.[5]
			• *Results:*
			  • 368 patients were eligible for analysis; they were treated with HCQ (n=97), HCQ plus AZM (n=113), or no HCQ (n=158). The median age for the patients in each group was 70, 68, and 69 years, respectively. All patients were male.
			  • 70 patients died; 35 of those who died (50%) were not receiving mechanical ventilation .
			  • No difference was observed between the groups in the risk of mechanical ventilation.
			  • Compared to the no HCQ group, the risk of death from any cause was higher in the HCQ group (adjusted HR: 2.61; 95% CI, 1.10–6.17; P = 0.03), but not in the HCQ plus AZM group (adjusted HR: 1.14; 95% CI, 0.56–2.32, P = 0.72).
			  • There was no between-group difference in the risk of death after ventilation.
			• *Limitations:*
			  • All male patient population.
			  • The dose and duration of administration of HCQ and AZM are not clarified. Patients were included if they received a single dose of either or both drugs.
			  • Propensity score adjustment was used to account for differences between the groups, but the possibility of residual confounding cannot be excluded as patients who were more ill may have been more likely to receive HCQ.
			  • No imaging data were presented; severity of chest X-ray findings could predict worse outcomes.
			  • Use of other antiviral or immune modulatory agents were not reported.
			  • The reason for the high mortality in patients who did not receive mechanical ventilation is not clear, especially as most of these patients appear to have had mild/moderate disease on admission.
			• *Interpretation:* This study showed no beneficial effect of HCQ plus AZM and a possible association of HCQ with increased mortality; however, residual confounding may have affected the study results.
			Randomized, Controlled Trial of HCQ vs. SOC (*This study has not been peer reviewed.*)[11]
			• This multicenter, randomized, open-label trial compared HCQ 1,200 mg once daily for 3 days followed by HCQ 800 mg once daily for the rest of the treatment duration (2 weeks for patients with mild/moderate COVID-19 [99%] and 3 weeks for one patient with severe disease) versus SOC.
			• The primary outcome was negative PCR within 28 days. Secondary outcomes were alleviation of symptoms (resolution of fever, SpO_2 > 94% on room air, resolution of respiratory symptoms) and improvement of markers of inflammation (including CRP) and chest X-ray within 28 days. Secondary outcomes for severe cases included all-cause mortality, clinical status, days of mechanical ventilation, ECMO, supplemental oxygenation, and hospital stay.

Drug Name	FDA-Approved Indications	Preclinical Data/ Mechanism of Action	Clinical Data to Date (Find clinical trials on *ClinicalTrials.gov*)
Hydroxychloroquine, continued			• *Results:*
			• 75 patients were enrolled in each study arm. Patients were randomized at a mean of 16.6 days after symptom onset.
			• No difference was found between the HCQ and SOC arms in negative PCR conversion rate within 28 days (85.4% vs.81.3% of participants, respectively) or in time to negative conversion (median 8 vs. 7 days, respectively).
			• There was no difference in negative conversion rate by age, body mass index, comorbid conditions, days between symptom onset and randomization, or other conditions analyzed.
			• There was no between-group difference in rate of symptom alleviation in the intention-to-treat analysis.
			• There was more rapid normalization of CRP and lymphocytopenia in the HCQ group.
			• AEs: 30% of participants in the HCQ arm (most commonly diarrhea) versus 8.8% of participants in the SOC arm.
			• *Limitations:*
			• The definition of SOC and use of concomitant medications (two patients received AZM) were not clearly stated.
			• It is unclear how the overall rate of symptom alleviation was calculated.
			• The duration of HCQ use (2 weeks) was longer than in most other observational cohort or clinical trials for the treatment of COVID-19.
			• The authors note that HCQ was associated with increased alleviation of symptoms (HR 8.83; 95% CI, 1.09-71.3), but this was only in post-hoc subgroup analysis excluding patients on other antivirals.
			• *Interpretation:* This study demonstrated no difference in viral clearance between HCQ and SOC.
			Observational Cohort of HCQ vs. No HCQ (*This study has not been peer reviewed.*)[12]
			• This observational, retrospective cohort study analyzed data for adult patients hospitalized for COVID-19 pneumonia at four French tertiary care centers over a 2-week period (March 17–31, 2020). Patients were eligible if they required oxygen by mask or nasal cannula. Patients were excluded if they were immediately admitted to the ICU or admitted with ARDS (requiring non-invasive ventilation or mechanical ventilation). The treatment arms compared were initiation of HCQ at a daily dose of 600 mg within 48 hours of admission and the absence of HCQ during the same period. The primary outcome was a composite of transfer to the ICU within 7 days of enrollment and/or death from any cause. An inverse probability of treatment weighting approach was used to "emulate" randomization.

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

Hydroxychloroquine, continued			• *Results:*
			  • 181 patients were eligible for the analysis: 84 patients received HCQ and 97 did not.
			  • Comorbidities were less common in the HCQ group; overall initial COVID-19 severity was well balanced across the treatment arms.
			  • In the HCQ group, 20% of the patients received concomitant AZM and 76% received amoxicillin/clavulanic acid.
			  • In the inverse probability of treatment weighting analysis there was no difference in the composite outcome between the HCQ group (20.5%) and the non-HCQ group (22.1%). Similarly, there was no difference in the secondary outcomes of all-cause mortality and development of ARDS.
			  • Among the 84 patients receiving HCQ, eight patients (9.5%) experienced ECG changes requiring treatment discontinuation at a median of 4 days from start of dosing, including seven patients with a QTc that prolonged >60 ms and one patient with new onset first-degree AV block.
			• *Limitations:*
			  • This was a retrospective, non-randomized study.
			  • The number of patients with QTc prolongation who received HCQ versus HCQ plus AZM (20% of all patients) was not reported.
			• *Interpretation:* In this retrospective study, there was no difference in clinically important outcomes between patients who received HCQ within 48 hours of hospital admission and those who did not.
			Randomized Controlled Trial of HCQ Plus Standard Treatment vs. Standard Treatment Alone (*This study has not been peer reviewed.*)[13]
			• In a randomized controlled trial in China, 62 hospitalized patients with mild (SaO_2/SpO_2 ratio > 93% or PaO_2/FIO_2 ratio >300 mm Hg) CT-confirmed COVID-19 pneumonia were randomized to HCQ 200 mg twice daily for 5 days plus standard treatment or to standard treatment only. Standard treatment included oxygen therapy, antiviral and antibacterial therapy, and immunoglobin, with or without corticosteroids.
			• *Results:*
			  • Compared to the control patients, the HCQ-treated patients had a 1 day-shorter mean duration of fever (2.2 days vs. 3.2 days) and cough (2.0 days vs. 3.1 days).
			  • 13% of the control patients and none of the HCQ-treated patients experienced progression of illness.
			  • 80.6% of HCQ-treated patients and 54.8% of control patients experienced either moderate or significant improvement in chest CT scan.
			  • AEs (1 rash, 1 headache) occurred among two of the HCQ-treated patients (6.4%); none occurred among the control 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 trial had a small sample size and short follow-up.
			  • Standard treatment is complex and not well defined.
			  • The presence and distribution of associated comorbidities (e.g., HTN, DM, lung disease) was not reported.
			  • There was no indication that radiologists were blinded to the treatment status of the patients, which could have biased determination of the chest CT outcome.
			• *Interpretation:* The methodological limitations of this study preclude determination of efficacy for HCQ.
			A Case Series of HCQ vs. Control[14]
			• In a case series from France, 26 hospitalized adults with SARS-CoV-2 infection categorized as asymptomatic or with upper or lower respiratory tract infection who received HCQ 200 mg three times daily for 10 days were compared to 16 control individuals (i.e., who refused treatment, did not meet eligibility criteria, or were from a different clinic).
			• *Results:*
			  • Six patients in the HCQ group were excluded from the analysis for the following reasons:
			    • One died.
			    • Three were transferred to the ICU.
			    • One stopped the study drug due to nausea.
			    • One withdrew from the study.
			  • Six patients also received AZM.
			  • By Day 6, NP PCRs were negative in 14 of 20 HCQ-treated patients (70%) and two of 16 controls (12.5%).
			  • Among the HCQ patients, eight of 14 (57.1%) who received only HCQ and six of six (100%) who received HCQ and AZM had negative NP PCRs by Day 6.
			  • Clinical outcomes for all patients were not reported.
			• *Limitations:* There are several methodologic concerns with this case series:
			  • The small sample size of the series.
			  • The criteria for enrollment of cases and controls is unclear.
			  • Asymptomatic individuals were enrolled.
			  • Exclusion of six HCQ-treated patients includes one death and three ICU transfers.
			  • No clinical outcomes were reported; thus, the clinical significance of a negative PCR is unknown.

Drug Name	FDA-Approved Indications	Preclinical Data/ Mechanism of Action	Clinical Data to Date (Find clinical trials on *ClinicalTrials.gov*)
Hydroxychloroquine, continued			• 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 plus Hydroxychloroquine section above.	See the Azithromycin plus Hydroxychloroquine section above.	**Case Series of HCQ Plus AZM**[15]
			
			• In a case series of 80 hospitalized patients with COVID-19 (including six patients from a previous study),[16] patients were treated with HCQ 200 mg three times daily for 10 days plus AZM 500 mg for 1 day followed by 250 mg once daily for 4 days. Mean time from symptom onset to treatment was about 5 days. Outcomes evaluated included the need for oxygen therapy or ICU transfer after ≥3 days of therapy, SARS-CoV-2 level by PCR, SARS-CoV-2 culture (in a subset of patients; a convenience sample), and length of stay in the infectious diseases ward.
			
			• *Clinical Results:*
			
			  • One patient died (1.2%), three required ICU transfer (3.8%), and 12 required oxygen therapy (15%).
			
			  • 65 patients (81.2%) were discharged to home or transferred to other units for continuing treatment; 14 patients (17.4%) remained hospitalized at the time the study results were published.
			
			• *Laboratory Results:*
			
			  • NP SARS-CoV-2 PCR was negative in 83% of patients by Day 7 and in 93% of patients by Day 8.
			
			  • In the subset of patients who had respiratory sample viral cultures performed at Day 5, results were negative for 97.5% of the samples.
			
			• *Limitations:*
			
			  • The trial's lack of a control group, which is particularly important because many people with mild disease improve in the absence of treatment.
			
			  • The definition of "discharge" varied.
			
			  • The lack of complete or longer-term follow-up.
			
			• *Interpretation:* The multiple issues with trial design and lack of a comparison group limit the usefulness of this study to inform recommendations.
			
			Small Prospective Case Series of HCQ Plus AZM[17]
			
			• A prospective case series from France assessed eleven consecutive hospitalized patients with COVID-19.
			
			• *Results:*
			
			  • Eight of the 11 patients had significant co-morbid conditions: obesity (2), solid cancer (3), hematological cancer (2), and HIV infection (1).

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

Hydroxychloroquine plus Azithromycin, continued			• Ten of 11 patients were receiving supplemental oxygen upon treatment initiation.
			
			• All patients were treated with HCQ 600 mg once daily for 10 days and AZM 500 mg once daily for 1 day followed by 250 mg once daily for 4 days.
			
			• Within 5 days, the condition of three patients worsened, including one patient who died and two patients who were transferred to the ICU.
			
			• AEs: HCQ was discontinued in one patient due to QTc prolongation.
			
			• Qualitative NP PCR remained positive at Days 5 and 6 after treatment initiation in eight of 10 patients.
			
			• *Limitations:* This is a case series that included few 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[18]
			
			• A case series in the United States reported changes in QTc interval in 84 patients with COVID-19 who received the combination of HCQ (400 mg twice daily for 1 day, followed by 200 mg twice daily for 4 days) and AZM (500 mg once daily for 5 days).
			
			• *Results:*
			  • 84 patients, 74% male, mean age 63 ± 15 years, 65% had HTN, mean serum creatinine 1.4 mg/dL at baseline, 13% required vasopressors, 11% had CAD.
			  • Concomitant drugs that may prolong QTc interval: 11% of participants on neuropsychiatric drugs and 8% of participants received levofloxacin, lopinavir/ritonavir or tacrolimus.
			  • Four patients died, without arrhythmia.
			  • Mean baseline QTc was 435 ± 24 ms, mean maximum QTc was 463 ± 32 ms.
			  • Mean time to maximum QTc was 3.6 ± 1.6 days, ECG follow-up was done for a mean of 4.3 days.
			  • Nine patients (11%) developed QTc >500 ms; the QTc increased by 40 to 60 ms and >60 ms in 18% and 12% of patients, respectively.
			
			• *Limitations:*
			  • Case series, descriptive
			
			• *Interpretation:* This case series demonstrates that HCQ and AZM in combination can prolong QTc and that use of the combination warrants careful monitoring.

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

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[19]
		
		• *In vitro* data does not support the use of DRV/c for the treatment of COVID-19.[20]
			Randomized Controlled Trial of LPV/r vs. SOC
			
			In a clinical trial that randomized 199 patients to LPV/r 400 mg/100 mg PO twice daily for 14 days or to SOC, patients randomized to the LPV/r arm did not have a shorter time to clinical improvement.
			
			• *Results:*
			  • There was a lower, but not statistically significant, mortality rate for those on LPV/r (19.2%) versus on SOC (25.0%) and shorter ICU stay for those given LPV/r compared to those given SOC (6 days vs. 11 days; difference = -5 days; 95% CI, -9 to 0).
			  • The duration of hospital stays and time to clearance of viral RNA from respiratory tract samples did not differ between the LPV/r and SOC arms.
			  • Nausea, vomiting, and diarrhea were all more frequent in the LPV/r-treated group.
			  • The study was powered only to show a fairly large effect.
			• *Limitations:*
			  • The study was not blinded, which may have affected the assessments of clinical improvement.
			  • The study was underpowered to show small effects.
			• *Interpretation:* A moderate-sized randomized trial failed to find a virologic or clinical benefit of LPV/r over SOC.
			
			LPV/r vs. Arbidol vs. SOC[21] (*This study has not been peer reviewed.*)
			
			• In a trial of 86 hospitalized patients with mild-to-moderate COVID-19, 34 patients were randomized to LPV/r, 35 patients to the broad-spectrum antiviral Arbidol (available in Russia), and 17 patients to SOC.
			• *Results* (comparison of LPV/r to SOC):
			  • The time to a negative SARS-CoV-2 nucleic acid pharyngeal swab was similar for patients receiving LPV/r (mean 9 days [SD 5.0]) and for those receiving SOC (mean 9.3 days [SD 5.2]).
			  • Progression to severe/critical status occurred among eight (24%) patients receiving LPV/r and two patients (12%) on SOC.
			• *Limitations:*
			  • Small sample size.
			  • The effectiveness of Arbidol in treating COVID-19 is unknown.
			• *Interpretation:* The small sample size limits the usefulness of this trial.
			
			LPV/r vs. CQ
			
			A small randomized study in China compared LPV/r to CQ. Please refer to the CQ section for the study description.

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

Remdesivir (GS-5734)	• Not approved by FDA
	
	• Investigational antiviral agent
		• Adenosine nucleotide analog prodrug that undergoes hydrolysis to its active form, which inhibits viral RNA-dependent RNA polymerase[22]
		
		• Potent *in vitro* activity demonstrated in SARS-CoV-2-infected Vero E6 cells[23]
		
		• In a rhesus macaque model of SARS-CoV-2 infection, animals who were started on RDV soon after inoculation had lower lung virus levels and less lung damage than control animals.[24]
			Multinational Randomized Controlled Trial of RDV vs. Placebo in Hospitalized Patients (*These data have not been peer reviewed.*)
			
			• The Adaptive COVID-19 Treatment Trial (ACTT) is an NIH-sponsored international, randomized, double-blind trial of RDV versus placebo (1:1 randomization ratio) in hospitalized adult patients (aged ≥18 years) with laboratory confirmed COVID-19 who have at least one of the following clinical manifestations: pulmonary infiltrates by radiographic imaging, SpO_2 ≤ 94% on ambient air, or require supplemental oxygen or mechanical ventilation. The study excluded people with ALT or AST level >5 times ULN or eGFR <30 ml/min, and people who were pregnant or breastfeeding. The primary study endpoint was time to recovery. Preliminary data were released on April 29, 2020, after an interim review by the study's DSMB. 1,063 participants enrolled into the study. Participants who received RDV had a 31% faster time to recovery than those who received placebo (median recovery time of 11 days vs 15 days, respectively; HR 1.31; 95% CI, 1.12 to 1.54, $P < 0.001$).[25] The results also showed a mortality rate of 8.0% versus 11.6% for the RDV and placebo groups, respectively ($P = 0.059$). Additional results (including analyses of important patient subgroups) are expected soon.[26]
			
			• *Limitations:* Only the preliminary analysis is available after the DSMB review. A full report of study results is still forthcoming.
			
			• *Interpretation:* First randomized, double-blinded, fully powered study to demonstrate the clinical benefit of a pharmacological treatment for COVID-19.
			
			Randomized Controlled Trial of RDV vs. Placebo for Severe COVID-19 in China[27]
			
			• Multicenter, double-blind, randomized, placebo-controlled trial in patients with severe COVID-19 in China. Patients were randomized 2:1 to IV RDV or normal saline placebo for 10 days. Concomitant use of LPV/r, corticosteroids, and interferons were allowed. The primary study endpoint was time to clinical improvement, defined as improvement on an ordinal scale or discharged alive from the hospital, whichever came first. The planned sample size was 453 patients.
			
			• Participant population: Hospitalized adults with laboratory confirmed COVID-19, symptom onset to randomization <12 days, O_2 saturation ≤ 94% on room air, or PaO_2/FiO_2 <300 mmHg, with radiographically confirmed pneumonia.
			
			• *Results:* Between February 6, 2020, and March 12, 2020, 237 hospitalized patients were enrolled and randomized to RDV (n = 158) or placebo (n = 79). The study was stopped before target enrollment was reached due to control of the COVID-19 outbreak in China.
			
			  • The participants' median age was 65 years, and 56% of the participants in the RDV arm and 65% in the placebo arm were male.
			
			  • There were more patients with HTN, DM, or CAD in the RDV arm than in the placebo arm.

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

Remdesivir, continued (GS-5734)			• At Day 1, 83% of the patients required supplemental oxygen by nasal cannula or mask; only one patient required mechanical ventilation or ECMO.
			
			• Median time from symptom onset to randomization was 9 days in the RDV group and 10 days in the placebo group.
			
			• 65% of the patients in the RDV group and 68% of patients in the placebo group received corticosteroids.
			
			• 28% to 29% of participants in each arm received LPV/r.
			
			• 29% of participants in the RDV arm, and 38% of participants in the placebo arm received interferon alfa 2b.
			
			• *Study endpoints:*
			
			  • There was no difference in the time to clinical improvement: a median of 21 days in RDV group versus 23 days in placebo group (HR 1.23; 95% CI, 0.87-1.75).
			
			  • Though not statistically significant, 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]).
			
			  • 28-day mortality was similar in the two arms: 14% of participants in RDV arm versus 13% in placebo arm.
			
			  • There was no difference in SARS-CoV-2 viral load at baseline; the rate of decline over time was similar between the two groups.
			
			  • The number of participants who had AEs was similar between the two groups (66% in RDV arm and 64% in placebo arm).
			
			  • More participants in the RDV arm discontinued therapy due to AEs (12% in RDV group vs. 5% in placebo group).
			
			• *Limitations:*
			
			  • The study was terminated early; as a result, the sample size did not have sufficient power to detect differences in clinical outcomes.
			
			  • Use of concomitant medications (corticosteroids, LPV/r, interferon) may have obscured 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. The study was terminated early; consequently, the study sample size was too small to detect differences in clinical outcomes.
			
			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 use of RDV led to the improvement.[28]

Key: ACE2 = angiotensin-converting enzyme 2; AE = adverse effect; ALT = alanine transaminase; ARDS = acute respiratory distress syndrome; AST = aspartate transaminase; AV = atrioventricular; AZM = azithromycin; CAD = coronary artery disease; CI = confidence interval; COVID-19 = coronavirus disease 2019; CQ = chloroquine; CRP = C-reactive protein; CT = computerized tomography; DM = diabetes; DRV/c = darunavir/cobicistat; DSMB = data safety monitoring board; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; eGFR = glomerular filtration rate; FDA = Food and Drug Administration; HR = hazard ratio; HTN = hypertension; ICU = intensive care unit; IFN = interferon; IL = interleukin; IV = intravenous; HCQ = hydroxychloroquine; LPV/r = lopinavir/ritonavir; NIH = National Institutes of Health; NP = nasopharyngeal; OR = odds ratio; PCR = polymerase chain reaction; PO = orally; RDV = remdesivir; QTcF = corrected QT interval by Fredericia; 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

References

1. Azithromycin (ZITHROMAX) [package insert]. Food and Drug Administration. 2013. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/050710s039,050711s036,050784s023lbl.pdf. Accessed: April 8, 2020.

2. Gielen V, Johnston SL, Edwards MR. Azithromycin induces anti-viral responses in bronchial epithelial cells. *Eur Respir J*. 2010;36(3):646-654. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20150207.

3. Culic O, Erakovic V, Cepelak I, et al. Azithromycin modulates neutrophil function and circulating inflammatory mediators in healthy human subjects. *Eur J Pharmacol*. 2002;450(3):277-289. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12208321.

4. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends*. 2020;14(1):72-73. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32074550.

5. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) *in vitro*. *Cell Res*. 2020;30(3):269-271. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32020029.

6. Vincent MJ, Bergeron E, Benjannet S, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. *Virol J*. 2005;2:69. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16115318.

7. Borba MGS, Val FFA, Sampaio VS, et al. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial. *JAMA Netw Open*. 2020;3(4):e208857. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32339248.

8. Huang M, Tang T, Pang P, et al. Treating COVID-19 with chloroquine. *J Mol Cell Biol*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32236562.

9. Hydroxychloroquine sulfate (PLAQUENIL)[package insert]. Food and Drug Administration. 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/009768s037s045s047lbl.pdf. Accessed: April 8, 2020.

10. Magagnoli J, Narendran S, Pereira F, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. *medRxiv*. 2020;[Preprint]. Available at: https://www.medRxiv.org/content/10.1101/2020.04.16.20065920v2.

11. Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with COVID-19: an open-label, randomized, controlled trial. *medRxiv*. 2020;[Preprint]. Available at: https://www.medRxiv.org/content/10.1101/2020.04.10.20060558v1.

12. Mahevas M, Tran V, Roumier M, et al. No evidence of clinical efficacy of hydroxychloroquine in patients hospitalized for COVID-19 infection with oxygen requirement: results of a study using routinely collected data to emulate a target trial. *medRxiv*. 2020;[Preprint]. Available at: https://www.medRxiv.org/content/10.1101/2020.04.10.20060699v1.

13. Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. *medRxiv*. 2020;[Preprint]. Available at: https://www.medRxiv.org/content/10.1101/2020.03.22.20040758v2.

14. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents*. 2020:105949. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32205204.

15. Gautret P, Lagier JC, Parola P, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study. *Travel Med Infect Dis*. 2020:101663. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32289548.

16. Gautret P, Lagier J, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *International Journal of Antimicrobial Agents*. 2020;[In press]. Available at: https://www.sciencedirect.com/science/article/pii/S0924857920300996.

17. Molina JM, Delaugerre C, Le Goff J, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. *Médecine et Maladies Infectieuses*. 2020;[In press]. Available at: https://www.sciencedirect.com/science/article/pii/S0399077X20300858?via%3Dihub#!

18. Chorin E, Dai M, Shulman E, et al. The QT interval in patients with COVID-19 treated with hydroxychloroquine and azithromycin. *Nature Medicine*. 2020. Available at: https://doi.org/10.1038/s41591-020-0888-2.

19. Nukoolkarn V, Lee VS, Malaisree M, Aruksakulwong O, Hannongbua S. Molecular dynamic simulations analysis of ritonavir and lopinavir as SARS-CoV 3CL(pro) inhibitors. *J Theor Biol*. 2008;254(4):861-867. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18706430.

20. De Meyer S, Bojkova D, Cinati J, et al. Lack of antiviral activity of darunavir against SARS-CoV-2. *medRxiv*. 2020;[Preprint]. Available at: https://www.medRxiv.org/content/10.1101/2020.04.03.20052548v1.

21. Li Y, Xie Z, Lin W, et al. An exploratory randomized, controlled study on the efficacy and safety of lopinavir/ritonavir or arbidol treating adult patients hospitalized with mild/moderate COVID-19 (ELACOI). *medRxiv*. 2020;[Preprint]. Available at: https://www.medRxiv.org/content/10.1101/2020.03.19.20038984v1.

22. Warren TK, Jordan R, Lo MK, et al. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. *Nature*. 2016;531(7594):381-385. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26934220.

23. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China. *Clin Infect Dis*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32176772.

24. Williamson BN, Feldmann F, Benjamin Schwarz B, et al. Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. *bioRxiv*. 2020;[Preprint]. Available at: https://www.biorxiv.org/content/10.1101/2020.04.15.043166v2.full.pdf.

25. Food and Drug Administration. Fact sheet for health care providers emergency use authorization (EUA) of remdesivir (GS-5734™). 2020. Available at: https://www.fda.gov/media/137566/download. Accessed May 8, 2020.

26. NIH clinical trial shows Remdesivir accelerates recovery from advanced COVID-19 [press release]. April 29, 2020.

27. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *The Lancet*. 2020. Available at: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31022-9/fulltext#seccestitle10.

28. Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe COVID-19. *N Engl J Med*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32275812.

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

(Last updated May 12, 2020)

- The information in this table is derived from data on the use of these drugs for FDA-approved indications or in investigational trials, and it is supplemented with data from patients with COVID-19 where available.
- The effective dosing of these drugs for the treatment of COVID-19 is unknown. Therefore, the doses listed below are primarily derived from FDA-approved indications or from clinical trials investigating therapies for COVID-19.
- There are limited or no data on dose modifications for patients with organ failure or those who require extracorporeal devices. Please refer to product labels, when available.
- Treatment-related AEs in patients with COVID-19 are not well defined; the validity of extrapolation between patient populations (i.e., FDA-approved use vs. COVID-19 use) is unknown, especially in critically ill patients. Reported AEs of these drugs that are associated with long-term therapy (i.e., months to years) are not included in this table because treatment for COVID-19 is not long term. Please refer to product labels, when available.
- There are currently not enough data to determine whether certain medications can be safely coadministered with therapies for the treatment of COVID-19. When using concomitant medications with similar toxicity profiles, consider additional safety monitoring.
- The potential additive, antagonistic, or synergistic effects and the safety of combination therapies for the treatment of COVID-19 are unknown. Clinicians are encouraged to report AEs to the FDA *Medwatch* program.
- For drug interaction information, please refer to product labeling, and visit the Liverpool COVID-19 Drug Interactions website.
- For information on drugs that prolong the QTc interval, please visit *CredibleMeds.org*.

Drug Name	Dosing Regimens *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Azithromycin (When Used with Hydroxychloroquine)	500 mg PO once on Day 1, then 250 mg PO daily on Days 2–5	Gastrointestinal effects (e.g., diarrhea, nausea, vomiting) Hepatotoxicity	Baseline/follow- up ECG Hepatic panel, SCr, potassium, magnesium	Additive effect with other drugs that prolong the QTc interval (including HCQ and CQ)	The Panel **recommends against** the use of HCQ plus AZM for the treatment of COVID-19 except in a clinical trial setting **(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	**Suggested Dose in EUA[a] for Adults/ Adolescents Weighing ≥50 kg:** • 1 gm PO once on Day 1, then 500 mg PO once daily for 4–7 days of total treatment based on clinical evaluation. **Per EUA:** • Some experts recommend a dose reduction of 50% for GFR <10 mL/min, hemodialysis, or peritoneal dialysis; no dose reduction is recommended for GFR >10 mL/min.	Prolonged QTc interval, Torsades de Pointes, AV block, ventricular arrhythmia Gastrointestinal effects (e.g., nausea, vomiting, diarrhea, hepatitis) Hypoglycemia Hemolysis (especially if G6PD deficient) Myopathy Rash Given the risk of heart rhythm problems, the FDA cautions against the use of CQ for COVID-19 outside the setting of a hospital or clinical trial.[1]	CBC, hepatic panel, blood glucose, SCr, potassium, magnesium Baseline/follow-up ECG if given with concomitant QTc-prolonging drugs or if underlying cardiac disease Perform G6PD testing; CQ **is not recommended** in patients with G6PD deficiency. Consider using HCQ instead of CQ while awaiting G6PD result.	Additive effect with other drugs that prolong the QTc interval (including AZM or cause hypoglycemia CYP2D6 inhibitor (moderate) P-gp inhibitor	There are insufficient data for the Panel to recommend for or against the use of CQ or the treatment of COVID-19 **(AIII)**. The Panel **recommends against** using high-dose CQ (600 mg twice daily for 10 days) for the treatment of COVID-19 **(AI)**. CQ is available through an EUA for hospitalized patients with COVID-19 who cannot access the drug via a clinical trial. Dose-dependent toxicity A list of clinical trials is available here: Chloroquine

Drug Name	Dosing Regimens *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Hydroxychloroquine	**Adults:** • Various loading and maintenance doses have been reported in studies or in clinical care. **Suggested Dose in EUA[a] for Hospitalized Adults/Adolescents Weighing ≥50 kg:** • 800 mg PO once on Day 1, then 400 mg PO once daily for 4–7 days of total treatment based on clinical evaluation. **Per EUA:** • Some experts recommend a dose reduction of 50% for GFR <10 mL/min, hemodialysis, or peritoneal dialysis; no dose reduction is recommended for GFR >10 mL/min **Infants, Children, and Adolescents** *Dose Options for Malaria Treatment:* • 13 mg/kg (maximum: 800 mg) PO followed by 6.5 mg/kg (maximum: 400 mg) PO at 6 hours, 24 hours, and 48 hours after initial dose; could extend for a total treatment duration of up to 5 days. • 6.5 mg/kg/dose (maximum: 400 mg/dose) PO BID on Day 1, followed by 3.25 mg/kg/dose (maximum: 200 mg/dose) PO BID for a total treatment duration of up to 5 days **Neonates:** • Dosing not established.	Prolonged QTc interval, Torsades de Pointes, AV block, ventricular arrhythmia Gastrointestinal effects (e.g., nausea, vomiting, diarrhea, hepatitis) Hypoglycemia Myopathy Anxiety, agitation, hallucinations, psychosis Allergic reaction/rash Given the risk of heart rhythm problems, the FDA cautions against the use of HCQ for COVID-19 outside the setting of a hospital or clinical trial.[1]	CBC, hepatic panel, blood glucose, SCr, potassium, magnesium Baseline ECG Follow-up ECG if given with concomitant QTc prolonging drugs (e.g., AZM) or if underlying cardiac diseases	Additive effect with other drugs that prolong the QTc interval (including AZM) or cause hypoglycemia CYP2D6 inhibitor (moderate) P-gp inhibitor	There are insufficient data for the Panel to recommend for or against the use of HCQ for the treatment of COVID-19 **(AIII)**. The Panel **recommends against** the use of HCQ plus AZM for the treatment of COVID-19 except in a clinical trial setting **(AIII)**. Available through EUA for hospitalized patients who cannot access HCQ via clinical trials. Long elimination; half-life is 40–55 days. Dose-dependent toxicity A list of clinical trials is available here: [Hydroxychloroquine](#)

Drug Name	Dosing Regimens *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Lopinavir/Ritonavir	**Adults:** • Lopinavir 400 mg/ritonavir 100 mg PO twice daily for 10–14 days **Neonates Aged ≥14 Days with a PMA ≥42 Weeks and Children Aged <18 Years:** • Lopinavir 300 mg/m^2 plus ritonavir 75 mg/m^2 (maximum: lopinavir 400 mg/ritonavir 100 mg per dose) PO twice daily for a total of 7 days	Nausea, vomiting, diarrhea Transaminase elevation QTc interval prolongation and Torsades de Pointes have been reported. PR interval prolongation	HIV antigen/antibody testing at baseline Serum transaminase levels Consider monitoring ECG when given with other QTc-prolonging medications.	**High Drug Interaction Potential** *Lopinavir:* • CYP3A4 inhibitor and substrate *Ritonavir:* • CYP3A4 > 2D6 substrate • Potent CYP3A4 and 2D6 inhibitor • Inducer of UGT1A1 and CYPs 1A2, 2C8, 2C9, and 2C19	The Panel **recommends against** the use of lopinavir/ritonavir and other HIV PIs for the treatment of COVID-19 except in a clinical trial setting **(AI)**. Liquid formulation commercially available. Crushing lopinavir/ritonavir 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 *Investigational drug (Remdesivir is not approved by the FDA; however, it is available through an EUA,[b] clinical trial, or the manufacturer's emergency access program).*	**In Patients Participating in Clinical Trials:** • Dose according to clinical trial protocol **Suggested Dose in EUA[b] for Adult and Pediatric Patients Weighing ≥40 kg** *Requiring Invasive Mechanical Ventilation and/or ECMO:* • 200 mg IV over 30-120 minutes for 1 dose on Day 1, followed by 100 mg IV daily over 30–120 minutes on Day 2 through Day 10 *Not Requiring Invasive Mechanical Ventilation and/or ECMO:* • 200 mg IV over 30-120 minutes for 1 dose on Day 1, followed by 100 mg IV daily over 30-120 minutes on Days 2 through 5. If no clinical improvement, may extend treatment for up to 5 additional days (for a total treatment duration of 10 days) **Suggested Dose in EUA[b] for Pediatric Patients Weighing 3.5 to <40 kg** *Requiring Invasive Mechanical Ventilation and/or ECMO:* • 5 mg/kg mg IV over 30-120 minutes for 1 dose on Day 1, followed by 2.5 mg/kg IV daily over 30-120 minutes on Day 2 through Day 10 *Not Requiring Invasive Mechanical Ventilation and/or ECMO:* • 5 mg/kg mg IV over 30–120 minutes for 1 dose on Day 1, followed by 2.5 mg/kg IV daily over 30-120 minutes on Day 2 through Day 5. If no clinical improvement, may extend treatment for up to 5 additional days (for a total treatment duration of 10 days)	Transient elevations in ALT or AST (Grade 1 or 2), typically after multiple days of therapy[3] Mild, reversible PT prolongation without INR change or hepatic effects[3] Drug vehicle is SBECD, which has been associated with renal toxicity. Potential for SBECD accumulation in patients with moderate to severe renal impairment Gastrointestinal symptoms (e.g., nausea, vomiting)	Monitor for infusion reactions. Renal and hepatic function **Do not administer** RDV if eGFR <30 mL/min (or receiving dialysis), or if ALT or AST is >5 times ULN	RDV levels are unlikely to be markedly altered by CYP2C8, CYP2D6, or CYP3A4 enzymes, or by P-gp or OATP drug transporters. RDV may be administered with weak to moderate inducers or with strong inhibitors of CYP450, OATP or P-gp. **Strong induction** of P-gp is expected to modestly reduce RDV levels. The clinical relevance of lower RDV levels is unknown. The use of RDV with known inducers of P-gp (e.g., rifampin) **is not recommended**.	On the basis of preliminary clinical trial data, the Panel recommends the investigational antiviral agent RDV for the treatment of COVID-19 in hospitalized patients with severe disease defined as SpO$_2$ ≤94% on ambient air (at sea level), requiring supplemental oxygen, mechanical ventilation, or ECMO **(BI)**. The Panel **does not recommend** RDV for the treatment of mild or moderate COVID-19 outside of a clinical trial **(AIII)**. RDV is available through an EUA[b] for the treatment of hospitalized adults and children with severe COVID-19. RDV is also available for other patient populations through expanded access and compassionate use programs. A list of clinical trials is available here: Remdesivir

a The EUA authorizes the use of these drugs from the SNS for treatment of hospitalized adolescent and adult COVID-19 patients weighing ≥50 kg and for whom a clinical trial is not available or for whom participation is not feasible.

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

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

References

1. Food and Drug Administration. FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems. 2020. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or. Accessed: May 8, 2020.

2. Best BM, Capparelli EV, Diep H, et al. Pharmacokinetics of lopinavir/ritonavir crushed versus whole tablets in children. *J Acquir Immune Defic Syndr*. 2011;58(4):385-391. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21876444.

3. Remdesivir (GS-5734) Investigator's Brochure. Edition 5. Gilead Sciences. February 21, 2020.

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

(Last updated May 12, 2020)

<table>
<tr><td colspan="2">**Summary Recommendations**</td></tr>
<tr><td colspan="2">**There are no Food and Drug Administration-approved drugs for the treatment of COVID-19.** Although reports have appeared in the medical literature and the lay press have claimed that patients with COVID-19 have been successfully treated with a variety of agents, definitive clinical trial data are needed to identify safe and effective treatments for this disease. Recommended clinical management of patients with COVID-19 includes infection prevention and control measures and supportive care, including supplemental oxygen and mechanical ventilatory support when indicated. As in the management of any disease, treatment decisions ultimately reside with the patient and their health care provider.

Immune-Based Therapy:

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

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of **non-SARS-CoV-2-specific intravenous immune globulin (IVIG)** for the treatment of COVID-19, except in the context of a clinical trial **(AIII)**. This should not preclude the use of IVIG when it is otherwise indicated for the treatment of complications that arise during the course of COVID-19.

- There are insufficient data to recommend either for or against the use of the following agents for the treatment of COVID-19 **(AIII)**:
  - **Interleukin-1 inhibitors** (e.g., **anakinra**)
  - **Interleukin-6 inhibitors** (e.g., **sarilumab**, **siltuximab**, **tocilizumab**)

- Except in the context of a clinical trial, the Panel **recommends against** the use of other immunomodulators, such as:
  - **Interferons (AIII)**, because of the lack of efficacy in treatment of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) and toxicity.
  - **Janus kinase inhibitors** (e.g., **baricitinib**) **(AIII)**, because of their broad immunosuppressive effect.</td></tr>
<tr><td colspan="2">**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional</td></tr>
<tr><td colspan="2">**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</td></tr>
</table>

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

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

Interleukin-1 and Interleukin-6 Inhibitors and Other Immunomodulators

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

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

References

1. Pedersen SF, Ho Y. SARS-CoV-2: A storm is raging. *The Journal of Clinical Investigation*. 2020. [In Press]. Available at: https://www.jci.org/articles/view/137647.

2. Ramos-Casals M, Brito-Zeron P, Lopez-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. *Lancet*. 2014;383(9927):1503-1516. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24290661.

3. Seguin A, Galicier L, Boutboul D, Lemiale V, Azoulay E. Pulmonary involvement in patients with hemophagocytic lymphohistiocytosis. *Chest*. 2016;149(5):1294-1301. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26836913.

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

5. Shakoory B, Carcillo JA, Chatham WW, et al. Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of macrophage activation syndrome: reanalysis of a prior Phase III trial. *Crit Care Med*. 2016;44(2):275-281. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26584195.

6. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395(10229):1033-1034. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32192578.

Convalescent Plasma and Immune Globulins

(Last updated May 12, 2020)

Recommendation:

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

Rationale for Recommendation

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

Rationale for Use in Patients with COVID-19

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

Clinical Data for COVID-19

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

Clinical Data for Other Viral Infections

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

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

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

Clinical Trials and Access

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

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

Adverse Effects

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

Considerations in Pregnancy

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

Considerations in Children

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

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

Recommendation:

- The COVID-19 Treatment Guidelines Panel **recommends against** the use of **non-SARS-CoV-2-specific intravenous immune globulin (IVIG)** for the treatment of COVID-19, except in the context of a clinical trial **(AIII)**. This should not preclude the use of IVIG when it is otherwise indicated for the treatment of complications that arise during the course of COVID-19.

Rationale for Recommendation

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

Clinical Data for COVID-19

These data have not been peer reviewed.

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

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

References

1. Wang X, Guo X, Xin Q, et al. Neutralizing antibodies responses to SARS-CoV-2 in COVID-19 inpatients and convalescent patients. *medRxiv*. 2020. [Preprint]. Available at: https://www.medrxiv.org/content/10.1101/2020.04.15.20065623v3.

2. Ahn JY, Sohn Y, Lee SH, et al. Use of convalescent plasma therapy in two COVID-19 patients with acute respiratory distress syndrome in Korea. *J Korean Med Sci*. 2020;35(14):e149. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32281317.

3. Pei S, Yuan X, Zhang Z, et al. Convalescent plasma to treat COVID-19: Chinese strategy and experiences. *medRxiv*. 2020. [Preprint]. Available at: https://www.medrxiv.org/content/10.1101/2020.04.07.20056440v1.

4. Ye M, Fu D, Ren Y, et al. Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. *J Med Virol*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32293713.

5. Zeng Q, Yu Z, Gou J, et al. Effect of convalescent plasma therapy on viral shedding and survival in COVID-19 patients. *The Journal of Infectious Diseases*. 2020. [Accepted Manuscript]. Available at: https://academic.oup.com/jid/advance-article/doi/10.1093/infdis/jiaa228/5826985.

6. Duan K, Liu B, Li C, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. *Proc Natl Acad Sci USA*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32253318.

7. Burnouf T, Radosevich M. Treatment of severe acute respiratory syndrome with convalescent plasma. *Hong Kong Med J*. 2003;9(4):309; author reply 310. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12904626.

8. Cheng Y, Wong R, Soo YO, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. *Eur J Clin Microbiol Infect Dis*. 2005;24(1):44-46. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15616839.

9. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. *J Infect Dis*. 2015;211(1):80-90. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25030060.

10. Narick C, Triulzi DJ, Yazer MH. Transfusion-associated circulatory overload after plasma transfusion. *Transfusion*. 2012;52(1):160-165. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21762464.

Interleukin-1 Inhibitors

(Last updated May 12, 2020)

Recommendation:

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

Rationale for Recommendation

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

Anakinra is a recombinant human IL-1 receptor antagonist. It is approved to treat rheumatoid arthritis and cryopyrin-associated periodic syndromes, and it is also used off-label for a variety of inflammatory conditions and severe chimeric antigen receptor T cell (CAR-T)-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 COVID-19 and other conditions, such as severe CAR-T-mediated CRS.

Clinical Data for COVID-19

A case series of anakinra use in moderate to severe COVID-19 pneumonia has recently been published. Details of the results of that study will be reported in the next update of these Guidelines.[1]

Clinical Trials

An open-label, randomized trial that is currently underway in Italy is comparing intravenous (IV) anakinra to IV emapalumab (an interferon gamma [IFNγ]-blocking antibody) for the treatment of COVID-19.

Adverse Effects

Anakinra was not associated with any significant safety concerns in trials of sepsis.[2-4] Increased rates of infection were reported with prolonged use in combination with tumor necrosis factor-alfa blockade, but not with short-term use.[5]

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.[6]

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 acute respiratory distress syndrome/sepsis are limited.

Drug Availability

Procuring anakinra may be a challenge at some hospitals in the United States. Anakinra is approved only in a subcutaneous formulation.

References

1. Aouba A, Baldolli A, Geffray L, et al. Targeting the inflammatory cascade with anakinra in moderate to severe COVID-19 pneumonia: case series. *Ann Rheum Dis*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32376597.

2. Fisher CJ, Jr., Dhainaut JF, Opal SM, et al. Recombinant human interleukin 1 receptor antagonist in the treatment of patients with sepsis syndrome. Results from a randomized, double-blind, placebo-controlled trial. Phase III rhIL-1ra Sepsis Syndrome Study Group. *JAMA*. 1994;271(23):1836-1843. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8196140.

3. Fisher CJ, Jr., Slotman GJ, Opal SM, et al. Initial evaluation of human recombinant interleukin-1 receptor antagonist in the treatment of sepsis syndrome: a randomized, open-label, placebo-controlled multicenter trial. *Crit Care Med*. 1994;22(1):12-21. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8124953.

4. Opal SM, Fisher CJ, Jr., Dhainaut JF, et al. Confirmatory interleukin-1 receptor antagonist trial in severe sepsis: a phase III, randomized, double-blind, placebo-controlled, multicenter trial. The Interleukin-1 Receptor Antagonist Sepsis Investigator Group. *Crit Care Med*. 1997;25(7):1115-1124. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9233735.

5. Winthrop KL, Mariette X, Silva JT, et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Soluble immune effector molecules [II]: agents targeting interleukins, immunoglobulins and complement factors). *Clin Microbiol Infect*. 2018;24 Suppl 2:S21-S40. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29447987.

6. Flint J, Panchal S, Hurrell A, et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-Part II: analgesics and other drugs used in rheumatology practice. *Rheumatology (Oxford)*. 2016;55(9):1698-1702. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26750125.

Interleukin-6 (IL-6) Inhibitors

(Last updated May 12, 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 **(AIII)**.

Rationale for Recommendation

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-CoV 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 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 ([NCT04315298](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, of the 226 critical patients, 28% in the sarilumab 400 mg group had died or were on a ventilator, compared with 46% in the sarilumab 200 mg group and 55% in the placebo group. Comparing mortality alone, 23% of those in the sarilumab 400 mg group died compared with 36% in the sarilumab 200 mg group and 27% in the placebo group. In contrast to the positive outcomes among critical patients, the April 27, 2020, press release about the study cited "negative trends" for most outcomes in severe patients.

Adverse Effects

The primary lab abnormalities that have been reported with sarilumab treatment are transient/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 if there is a drug-associated risk for major birth defects or miscarriage.

Drug Availability

The SQ formulation 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 for COVID-19

There are limited, unpublished data describing the efficacy of siltuximab in patients with COVID-19.[6] There are also no data describing clinical experiences using siltuximab for patients with other novel coronavirus infections (i.e., severe acute respiratory syndrome [SARS], Middle East respiratory syndrome [MERS]).

Clinical Trials

See *ClinicalTrials.gov* for a list of 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 three weeks.

Considerations in Pregnancy

There are insufficient data to determine if there is a drug-associated risk for major birth defects or miscarriage.

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 ([NCT04331808](#)) is an open-label, randomized trial of hospitalized patients with COVID-19 (n = 129 at seven sites in France) who were at a moderate or severe disease stage at study entry and who were randomized to receive tocilizumab (n = 65) or standard of care alone (n = 64). Patients received tocilizumab 8 mg/kg on Day 1. If there was no response (i.e., no decrease in oxygen requirement), a second infusion 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]

In an uncontrolled, retrospective cohort study, 21 hospitalized patients with COVID-19 who received tocilizumab reported improvement in oxygenation, systemic inflammation, and hypoxic respiratory failure. At study entry, 17 of the 21 patients had severe disease, and the remaining four had critical disease. The mean age was 56 years (range 25-88 years). All patients were febrile, had abnormal chest CT findings, and required oxygen supplementation (two required mechanical ventilation). The mean CRP level was 75 mg/L, the mean IL-6 expression level was 153 pg/mL, the mean D-dimer level was 0.80 µg/mL, and the mean lymphocyte percentage was 15.5%. Eighteen patients received tocilizumab IV infusion once, and three were dosed a second time for an indication of fever within 12 hours. Following administration of tocilizumab, fever normalized, lymphocyte percentage improved, and CRP level declined. Oxygen requirements were reduced by Day 5 in 15 of 20 participants (75%). There were no serious AEs attributed to the use of tocilizumab, and no concurrent bacterial, fungal or viral infection was observed during the treatment. It is difficult to assess the role of tocilizumab in this retrospective case series due to its small sample size and lack of a control group.[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 if there is a drug-associated risk for major birth defects or miscarriage. Monoclonal antibodies are actively transported across the placenta in the third trimester and may affect immune responses *in utero* in the exposed infant.

Considerations in Children

In children, tocilizumab is frequently used for CRS following CAR-T therapy,[10] and it is occasionally used for macrophage activation syndrome.[11] Pediatric data for its use in acute respiratory distress syndrome/sepsis are limited.

Drug Availability

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

References

1. Yoshikawa T, Hill T, Li K, Peters CJ, Tseng CT. Severe acute respiratory syndrome (SARS) coronavirus-induced lung epithelial cytokines exacerbate SARS pathogenesis by modulating intrinsic functions of monocyte-derived macrophages and dendritic cells. *J Virol*. 2009;83(7):3039-3048. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19004938.

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

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

4. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China. *Clin Infect Dis*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32176772.

5. Regeneron and Sanofi provide update on U.S. Phase 2/3 adaptive-designed trial of KEVZARA® (sarilumab) in hospitalized COVID-19 patients [press release]. 2020.

6. Gritti G, Raimondi F, Ripamonti D, et al. Use of siltuximab in patients with COVID-19 pneumonia requiring ventilatory support. *medRxiv*. 2020. Available at: https://www.medrxiv.org/content/10.1101/2020.04.01.20048561v1.

7. Le RQ, Li L, Yuan W, et al. F FDA approval summary: tocilizumab for treatment of chimeric antigen receptor T cell-induced severe or life-threatening cytokine release syndrome. *Oncologist*. 2018;23(8):943-947. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29622697.

8. Tocilizumab improves significantly clinical outcomes of patients with moderate or severe COVID-19 pneumonia [press release]. 2020.

9. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci USA*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32350134.

10. Gardner RA, Ceppi F, Rivers J, et al. Preemptive mitigation of CD19 CAR T-cell cytokine release syndrome without attenuation of antileukemic efficacy. *Blood*. 2019;134(24):2149-2158. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31697826.

11. Yokota S, Itoh Y, Morio T, Sumitomo N, Daimaru K, Minota S. Macrophage activation syndrome in patients with systemic juvenile idiopathic arthritis under treatment with tocilizumab. *J Rheumatol*. 2015;42(4):712-722. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25684767.

Other Immunomodulators

(Last updated May 12, 2020)

Interferons (Alfa, Beta)

Recommendation:

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

Rationale for Recommendation

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

Rationale for Use in Patients with COVID-19

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

Clinical Data for COVID-19

Interferon-beta used alone and in combination with ribavirin in patients with SARS and MERS has failed to show a significant positive effect on clinical outcomes.[1-5]

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

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

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

Adverse Effects

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

Drug-Drug Interactions

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

Considerations in Pregnancy

Data from several large pregnancy registries did not demonstrate an association between exposure to interferon-beta-1b preconception or during pregnancy and an increased risk of adverse birth outcomes

(e.g., spontaneous abortion, congenital anomaly), and exposure did not influence birth weight, height, or head circumference.

Considerations in Children

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

Janus Kinase Inhibitors (e.g., Baricitinib)

Recommendation:

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

Rationale for Recommendation

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

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

Rationale for Use in Patients with COVID-19

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

Clinical Data for COVID-19

No clinical data has been reported to date.

Adverse Effects

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

Considerations in Pregnancy

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

Corticosteroids

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

References

1. Al-Tawfiq JA, Momattin H, Dib J, Memish ZA. Ribavirin and interferon therapy in patients infected with the Middle East respiratory syndrome coronavirus: an observational study. *Int J Infect Dis*. 2014;20:42-46. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24406736.

2. Arabi YM, Shalhoub S, Mandourah Y, et al. Ribavirin and interferon therapy for critically ill patients with Middle East Respiratory Syndrome: a multicenter observational study. *Clin Infect Dis*. 2019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31925415.

3. Chu CM, Cheng VC, Hung IF, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax*. 2004;59(3):252-256. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14985565.

4. Omrani AS, Saad MM, Baig K, et al. Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: a retrospective cohort study. *Lancet Infect Dis*. 2014;14(11):1090-1095. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25278221.

5. Shalhoub S, Farahat F, Al-Jiffri A, et al. IFN-alfa2a or IFN-beta1a in combination with ribavirin to treat Middle East respiratory syndrome coronavirus pneumonia: a retrospective study. *J Antimicrob Chemother*. 2015;70(7):2129-2132. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25900158.

6. Ranieri VM, Pettila V, Karvonen MK, et al. Effect of intravenous interferon beta-1a on death and days free from mechanical ventilation among patients with moderate to severe acute respiratory distress syndrome: a randomized clinical trial. *JAMA*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32065831.

7. Genovese MC, Kremer J, Zamani O, et al. Baricitinib in patients with refractory rheumatoid arthritis. *N Engl J Med*. 2016;374(13):1243-1252. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27028914.

8. Smolen JS, Genovese MC, Takeuchi T, et al. Safety profile of baricitinib in patients with active rheumatoid arthritis with over 2 years median time in treatment. *J Rheumatol*. 2019;46(1):7-18. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30219772.

9. Dougados M, van der Heijde D, Chen YC, et al. Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: results from the RA-BUILD study. *Ann Rheum Dis*. 2017;76(1):88-95. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27689735.

10. Richardson P, Griffin I, Tucker C, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Lancet*. 2020;395(10223):e30-e31. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32032529.

11. Stebbing J, Phelan A, Griffin I, et al. COVID-19: combining antiviral and anti-inflammatory treatments. *Lancet Infect Dis*. 2020;20(4):400-402. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32113509.

12. Baricitinib (OLUMIANT) [prescribing information]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/207924s001lbl.pdf. Accessed: April 8, 2020.

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

(Last updated May 12, 2020)

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

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/ Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on *ClinicalTrials.gov*)
Blood Products			
COVID-19 Convalescent Plasma and SARS-CoV-2 Immune Globulins	Not approved by the FDA	Plasma donated from individuals who have recovered from COVID-19 includes antibodies to SARS-CoV-2.[1] Similarly, SARS-CoV-2 immune globulin is a concentrated antibody preparation derived from the plasma of people who have recovered from COVID-19. Both products may help suppress the virus and modify the inflammatory response.	**For COVID-19:** • Data supporting the use of convalescent plasma for COVID-19 are limited to a small retrospective cohort study, small case series, and case reports. • There are no clinical data on the use of SARS-CoV-2 immune globulin or hyperimmune globulin in COVID-19. **For Other Viruses:** • The use of convalescent plasma has been evaluated in other respiratory virus outbreaks, including H1N1 influenza, SARS, and viral diseases (e.g., SARS), with some suggestion of potential benefit.[2-9] No convalescent blood products are currently licensed by the FDA. • There are no clinical data on the use of specific immune globulin or hyperimmune globulin in patients with SARS or MERS.
Non-SARS-CoV-2 Specific Intravenous Immune Globulin	Primary immune disorders Thrombocytopenic purpura Kawasaki disease Motor neuropathy Prophylaxis of various bacterial and viral diseases	Passive immunity; human immunoglobulin is derived from pooled plasma of blood donors and contains antibodies against a broad spectrum of pathogens. Currently, only a small proportion of the U.S. population has been infected with SARS-CoV-2. Therefore, products derived from the plasma of donors who were not confirmed to have had SARS-CoV-2 infection are not likely to contain SARS-CoV-2 antibodies.	**For COVID-19** • *Not Peer Reviewed:* A retrospective, nonrandomized cohort study of IVIG in eight treatment centers in China between December 2019 and March 2020 found no difference in 28-day or 60-day mortality between the 174 patients who were treated with IVIG and the 151 patients who were not treated with IVIG. Patients who received IVIG were hospitalized for longer (median of 24 days vs. 16 days) and experienced longer duration of disease (median of 31 days vs. 23 days). It should be noted that a higher proportion of IVIG-treated patients had severe disease at study entry (71 [41%] with critical status in the IVIG group vs. 32 [21%] in the non-IVIG group). A subgroup analysis that was

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on *ClinicalTrials.gov*)
Blood Products, continued			
Non-SARS-CoV-2 Specific Intravenous Immune Globulin, continued			limited to the critical patients suggested a mortality benefit at 28 days, which was no longer significant at 60 days. The results are difficult to interpret because of important limitations in the study design. In particular, patients were not randomized to receive IVIG versus no IVIG, and the IVIG group was older, was more likely to have coronary heart disease, and had a higher proportion of patients with severe COVID-19 disease at study entry. Also, patients received numerous other concomitant therapies for COVID-19.[10]
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[11-13]	No clinical data for COVID-19. **For MERS:[14-17]** • Retrospective studies with IFN alfa-2a, IFN alfa-2b, or IFN beta-1a in combination with ribavirin showed no clear benefit. • Ribavirin plus IFN alfa-2a survival rates: 30% to 100% in three small studies (n < 20)[18] • Ribavirin plus IFN alfa-2a or IFN alfa-2b: No significant improvement in clinical outcome or survival at 28 days.[19] • Ribavirin plus IFN beta-1a SQ: Retrospective analyses showed no significant effect on clinical outcome.[14]
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)[11,21] Among IFN subtypes, IFN beta-1b shows greatest *in vitro* inhibition of MERS-CoV.[16,22] *In vitro* activity against MERS-CoV in lung cells.[20]	**Inhaled IFN beta-1a (SNG001):** • Phase 2 clinical trials showed improved lung function in asthma patients with respiratory infections.[20]
Interleukin-1 Inhibitor			
Anakinra	Rheumatoid arthritis Cryopyrin-associated periodic syndromes[23]	Competitively inhibits IL-1 binding to the interleukin-1 type I receptor	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_)
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[24]	Human recombinant monoclonal antibody IL-6 receptor antagonist[25]	**For COVID-19** • _Press Release:_ A Phase 2/3 randomized clinical trial (NCT04315298) of hospitalized COVID-19 patients. Preliminary data were released after an independent DMC recommended discontinuing the 200-mg arm and restricting future enrollment to critical patients only. Of the first 457 participants enrolled, 145 were randomized to sarilumab 400 mg, 136 to sarilumab 200 mg, and 77 to placebo. At study entry, 28% had severe illness, 49% had critical illness, and 23% had multisystem organ dysfunction. Sarilumab decreased CRP, which changed by -79%, -77%, and -21% in the sarilumab 400 mg group, sarilumab 200 mg group, and placebo group, respectively (primary outcome of the Phase 2 trial). Of the 226 critical patients, 28% in the sarilumab 400 mg group had died or were on a ventilator at the time of data analysis, compared with 46% in the sarilumab 200 mg group and 55% in the placebo group. Comparing mortality alone, 23% of those in the sarilumab 400 mg group died, compared with 36% in the sarilumab 200 mg group and 27% in the placebo group. In contrast to positive outcomes among critical patients, the press release cited "negative trends" for most outcomes in severe patients.[26]
Siltuximab	Multicentric Castleman disease	Human-mouse chimeric monoclonal antibody IL-6 antagonist[27]	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) and improved clinical condition following siltuximab (7 of 21). Other patients experienced no clinically relevant change in condition (9 of 21) or worsening condition (5 of 21). Of the five patients with worsening conditions, there was one death and one cerebrovascular event (median follow-up time of 8 days).

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*)
Tocilizumab	Cytokine release syndrome (induced by CAR T-cell therapy) Rheumatoid arthritis Giant cell arteritis Polyarticular juvenile idiopathic arthritis Systemic juvenile idiopathic arthritis[28]	Recombinant humanized monoclonal antibody IL-6 receptor antagonist	**For COVID-19** • *Press Release:* Early results from the CORIMUNO-TOCI trial (NCT04331808); open-label randomized trial of hospitalized patients with COVID-19 (n = 129; seven sites in France) at moderate or severe disease stage, who were randomized to receive tocilizumab (n = 65) or standard of care 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 compared with standard of care. Detailed results of the trial have not been reported. • An uncontrolled, retrospective cohort study of 21 hospitalized COVID-19 patients who received tocilizumab reported improvement in oxygenation, systemic inflammation, and hypoxic respiratory failure.[29] At study entry, 17 of the 21 patients had severe disease and four of the 21 patients had critical disease; mean age was 56 years (range 25–88), all patients were febrile, had abnormal chest CT findings, and required oxygen supplementation (two required mechanical ventilation). Mean CRP level was 75 mg/L, mean IL-6 expression level was 153 pg/mL, mean D-dimer level was 0.80 μg/mL, and mean lymphocyte percentage was 15.5%. Eighteen patients were given tocilizumab IV infusion once, and three were dosed a second time for indication of fever within 12 hours. Following tocilizumab administration, fever normalized, lymphocyte percentage improved, and CRP level declined. Oxygen requirements were reduced by Day 5 in 15 of 20 participants (75%). There were no serious AEs attributed to tocilizumab, and no concurrent infections (bacterial, fungal, or viral) 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.

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*)
Janus Kinase Inhibitor			
Baricitinib	Rheumatoid arthritis[30]	JAK inhibitor Inhibition of kinases that regulate endocytosis (AAK1 and GAK) Baricitinib is predicted to interfere with SARS-CoV-2 receptor-mediated endocytosis in lung AT2 alveolar epithelial cells.[31]	No clinical data for COVID-19, SARS, or MERS Baricitinib plasma concentrations are predicted to potentially be sufficient for AAK1 inhibition when administered at labeled dose (for the FDA-approved indication).[31]

Key: AAK1 = AP2-associated protein kinase 1; AE = adverse event; ARDS = acute respiratory distress syndrome; AT2 = alveolar type 2; CAR = chimeric antigen receptor; COVID-19 = coronavirus disease 2019; CRP = C-reactive protein; DMC = data monitoring committee; FDA = Food and Drug Administration; GAK = cyclin G-associated kinase; IL = interleukin; IV = intravenous; IVIG = intravenous immunoglobulin; JAK = Janus kinase inhibitor; MERS = Middle East respiratory syndrome; SARS = severe acute respiratory syndrome; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

References

1. Wang X, Guo X, Xin Q, et al. Neutralizing antibodies responses to SARS-CoV-2 in COVID-19 inpatients and convalescent patients. *medRxiv*. 2020:[Preprint]. Available at: https://www.medRxiv.org/content/10.1101/2020.04.15.20065623v3.

2. Beigel JH, Tebas P, Elie-Turenne MC, et al. Immune plasma for the treatment of severe influenza: an open-label, multicentre, phase 2 randomised study. *Lancet Respir Med*. 2017;5(6):500-511. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28522352.

3. Burnouf T, Radosevich M. Treatment of severe acute respiratory syndrome with convalescent plasma. *Hong Kong Med J*. 2003;9(4):309; author reply 310. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12904626.

4. Cheng Y, Wong R, Soo YO, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. *Eur J Clin Microbiol Infect Dis*. 2005;24(1):44-46. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15616839.

5. Chun S, Chung CR, Ha YE, et al. Possible transfusion-related acute lung injury following convalescent plasma transfusion in a patient with Middle East Respiratory Syndrome. *Ann Lab Med*. 2016;36(4):393-395. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27139619.

6. Kong L. Severe acute respiratory syndrome (SARS). *Transfus Apher Sci*. 2003;29(1):101. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12952008.

7. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. *J Infect Dis*. 2015;211(1):80-90. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25030060.

8. Soo YO, Cheng Y, Wong R, et al. Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients. *Clin Microbiol Infect*. 2004;10(7):676-678. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15214887.

9. Yeh KM, Chiueh TS, Siu LK, et al. Experience of using convalescent plasma for severe acute respiratory syndrome among healthcare workers in a Taiwan hospital. *J Antimicrob Chemother*. 2005;56(5):919-922. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16183666.

10. Shao Z, Feng Y, Zhong L, et al. Clinical efficacy of intravenous immunoglobulin therapy in critical patients with COVID-19: A multicenter retrospective cohort study. *Preprints with the Lancet*. 2020:[Preprint]. Available at: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3576827.

11. Spiegel M, Pichlmair A, Muhlberger E, Haller O, Weber F. The antiviral effect of interferon-beta against SARS-coronavirus is not mediated by MxA protein. *J Clin Virol*. 2004;30(3):211-213. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15135736.

12. interferon alfa-2b (INTRON A) [package insert]. Food and Drug Administration. 2018.Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103132Orig1s5199lbl.pdf. Accessed: May 9, 2020.

13. Peginterferon alfa-2a (PEGASYS) [prescribing information]. Food and Drug Administration. 2017.Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/103964s5270lbl.pdf. Accessed: May 9, 2020.

14. Shalhoub S, Farahat F, Al-Jiffri A, et al. IFN-alfa2a or IFN-beta1a in combination with ribavirin to treat Middle East respiratory syndrome coronavirus pneumonia: a retrospective study. *J Antimicrob Chemother*. 2015;70(7):2129-2132. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25900158.

15. Arabi YM, Asiri AY, Assiri AM, et al. Treatment of Middle East respiratory syndrome with a combination of lopinavir/ritonavir and interferon-beta1b (MIRACLE trial): statistical analysis plan for a recursive two-stage group sequential randomized controlled trial. *Trials*. 2020;21(1):8. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31900204.

16. Arabi YM, Shalhoub S, Mandourah Y, et al. Ribavirin and interferon therapy for critically ill patients with Middle East Respiratory Syndrome: a multicenter observational study. *Clin Infect Dis*. 2019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31925415.

17. Zumla A, Chan JF, Azhar EI, Hui DS, Yuen KY. Coronaviruses—drug discovery and therapeutic options. *Nat Rev Drug Discov*. 2016;15(5):327-347. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26868298.

18. Al-Tawfiq JA, Memish ZA. Update on therapeutic options for Middle East Respiratory Syndrome Coronavirus (MERS-CoV). *Expert Rev Anti Infect Ther*. 2017;15(3):269-275. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27937060.

19. Omrani AS, Saad MM, Baig K, et al. Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: a retrospective cohort study. *Lancet Infect Dis*. 2014;14(11):1090-1095. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25278221.

20. Schofield A. Synairgen to start trial of SNG001 in COVID-19. 2020. Available at: https://pharmafield.co.uk/pharma_news/synairgen-to-start-trial-of-sng001-in-covid-19/. Accessed May 9, 2020.

21. Haji Abdolvahab M, Mofrad MR, Schellekens H. Interferon beta: from molecular level to therapeutic effects. *Int Rev Cell Mol Biol*. 2016;326:343-372. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27572132.

22. Martinez MA. Compounds with therapeutic potential against novel respiratory 2019 coronavirus. *Antimicrob Agents Chemother*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32152082.

23. Kineret (anakinra) [package insert]. Food and Drug Administration. 2012. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103950s5136lbl.pdf. Accessed: May 5, 2020.

24. Sarilumab (KEVZARA) [prescribing information]. Food and Drug Administration. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761037s001lbl.pdf. Accessed May 9, 2020.

25. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China. *Clin Infect Dis*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32176772.

26. Regeneron and Sanofi provide update on U.S. Phase 2/3 adaptive-designed trial of KEVZARA® (sarilumab) in hospitalized COVID-19 patients [press release]. 2020.

27. SYLVANT (siltuximab) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125496s018lbl.pdf. Accessed: May 5, 2020.

28. Food and Drug Administration. ACTEMRA (tocilizumab) Prescribing Information. 2019.Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125276s127,125472s040lbl.pdf. Accessed: April 8, 2020.

29. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci U S A*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32350134.

30. Baricitinib (OLUMIANT) [prescribing information]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/207924s001lbl.pdf. Accessed: April 8, 2020.

31. Richardson P, Griffin I, Tucker C, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Lancet*. 2020;395(10223):e30-e31. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32032529.

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

(Last updated May 12, 2020)

- The information in this table is derived from data on the use of these drugs and biologic products for FDA-approved indications or from investigational trials; it is supplemented with data from patients with COVID-19 where available.

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

Drug Name	Dosing Regimen *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Blood Products, continued					
Non-SARS-CoV-2 Specific Intravenous Immune Globulin	Doses vary based on indication and formulation	Thrombotic events Renal dysfunction and acute renal failure (more common with certain products) Flu-like symptoms, dermatologic effects, arrhythmia, TRALI, anaphylaxis, aseptic meningitis, and hemolysis AEs may be predisposed by high dose, rapid infusion, or underlying conditions, including IgA-deficiency. AEs may vary between formulations. Consider the risks and benefits of the high-dose regimen in patients with increased risk of thrombosis, hemolysis, acute kidney injury, or volume overload.	Observe the patient and measure vital signs at baseline and during and after infusion. Discontinue if renal function deteriorates during treatment.	IVIG may interfere with immune response to certain vaccines.	The Panel **recommends against** the use of non-SARS-CoV-2 specific IVIG for the treatment of COVID-19, except in the context of a clinical trial **(AIII)**. This should not preclude the use of IVIG when otherwise indicated for treatment of complications that arise during COVID-19. A list of clinical trials is available here: Intravenous Immunoglobulin

Drug Name	Dosing Regimen *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Interferons					
Interferon Alfa	Peginterferon alfa-2a 180 mcg SQ once weekly for 2 weeks for MERS[2,3]	Flu-like symptoms (e.g., fever, fatigue, myalgia), injection site reactions, liver function abnormalities, decreased blood counts, worsening of depression, insomnia, irritability, nausea, vomiting, and hypertension[4]	CBC with differential LFTs (ALT); avoid if Child-Pugh Score >6 Depression, psychiatric symptoms Reduce dose in patients with CrCl <30 mL/min.	Low potential for drug interactions Inhibition of CYP1A2	The Panel **recommends against** the use of interferon alfa, except in the context of a clinical trial **(AIII)**. For MERS, SQ used in combination with ribavirin. Use 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 here: Interferon
Interferon Beta	**IFN Beta-1a:** • 44 mcg SQ three times weekly[3] for MERS • Duration unknown **IFN Beta-1b:** • 0.25 mg SQ every 48 hours for MERS[5] • Duration unknown **IFN Beta-1a:** • SNG001 (a formulation delivered by nebulization; not approved in the United States)	Flu-like symptoms (e.g., fever, fatigue, myalgia), leukopenia, neutropenia, thrombocytopenia, lymphopenia, increased liver enzymes (ALT > AST), injection site reactions, headache, hypertonia, pain, rash, and worsening of depression[6,7]	LFTs CBC with differential Worsening CHF Depression/suicidal ideation	Low potential for drug interactions	The Panel **recommends against** use of interferon beta, except in the context of a clinical trial **(AIII)**. Use caution with other hepatotoxic agents. Reduce dose if ALT >5 times ULN. Several products are available; doses differ between products. **IFN Beta-1a Products:** • Avonex, Rebif **IFN Beta-1b Products:** • Betaseron, Extavia **IFN Beta-1a Product:** • SNG001 (a formulation delivered by nebulization; not approved in United States) A list of clinical trials is available here: 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's Recommendations, Comments, and Links to Clinical Trials
Interleukin-1 Inhibitor					
Anakinra	Standard adult dose is 100 mg SQ once daily Duration unknown	Neutropenia (particularly in combination with other agents that can cause neutropenia) Anaphylaxis Headache, nausea, diarrhea, sinusitis, arthralgia, flu-like symptoms, and abdominal pain Injection site reactions	CBC Renal function (reduce dose in patients with CrCl <30 mL/min)	Use with TNF-blocking agents **is not recommended** due to increased risk of infection.	There are insufficient data for the Panel to recommend for or against the use of anakinra **(AIII)**. A list of clinical trials is available here: Anakinra
Interleukin-6 Inhibitors					
Sarilumab[8]	**Clinical Trial Dosing (See NCT04315298):** • 400 mg IV vs. placebo (single dose)[9] **Note:** The only FDA-approved sarilumab product is a SQ formulation.	Neutropenia, thrombocytopenia Gastrointestinal perforation HSR Increased ALT and AST Hepatitis B reactivation Infusion reaction possible	Monitor for HSR Monitor for infusion reaction Neutrophils, platelets, liver function	Elevated IL-6 may downregulate CYP enzymes; use of sarilumab may lead to increased metabolism of drugs that are CYP450 substrates. Effects on CYP450 may persist for weeks after therapy.	There are insufficient data for the Panel to recommend either for or against the use of sarilumab for the treatment of COVID-19 **(AIII)**. A list of clinical trials is available here: Sarilumab
Siltuximab	11 mg/kg IV over 1 hour every 3 weeks for multicentric Castleman disease[10] Dose and duration for COVID-19 unknown	Infusion-related reaction Gastrointestinal perforation Neutropenia Hypertension	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	There are insufficient data for the Panel to recommend for or against the use of siltuximab **(AIII)**. May mask signs of acute inflammation (i.e., suppression of fever and CRP)

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

Key: AE = adverse effect; ALT = alanine transaminase; AST = aspartate aminotransferase; CBC = complete blood count; CHF = congestive heart failure; COVID-19 = coronavirus disease 2019; CrCl = creatinine clearance; CYP = cytochrome P; FDA = Food and Drug Administration; HSR = hypersensitivity reaction; IFN = interferon; IND = Investigational New Drug Application; IV = intravenous; IVIG = intravenous immunoglobulin; LFT = liver function test; MERS = Middle East respiratory syndrome; OAT = organic anion transporter; the Panel = COVID-19 Treatment Guidelines Panel; PO = orally; SARS = severe acute respiratory syndrome; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SQ = subcutaneous; TACO = transfusion-related circulatory overload; TNF = tumor necrosis factor; TRALI = transfusion-related acute lung injury; ULN = upper limit of normal

References

1. Narick C, Triulzi DJ, Yazer MH. Transfusion-associated circulatory overload after plasma transfusion. *Transfusion*. 2012;52(1):160-165. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21762464.

2. Omrani AS, Saad MM, Baig K, et al. Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: a retrospective cohort study. *Lancet Infect Dis*. 2014;14(11):1090-1095. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25278221.

3. Shalhoub S, Farahat F, Al-Jiffri A, et al. IFN-alfa2a or IFN-beta1a in combination with ribavirin to treat Middle East respiratory syndrome coronavirus pneumonia: a retrospective study. *J Antimicrob Chemother*. 2015;70(7):2129-2132. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25900158.

4. Peginterferon alfa-2a (PEGASYS) [prescribing information]. Food and Drug Administration. 2017.Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/103964s5270lbl.pdf. Accessed: April 8, 2020.

5. Arabi YM, Asiri AY, Assiri AM, et al. Treatment of Middle East respiratory syndrome with a combination of lopinavir/ritonavir and interferon-beta1b (MIRACLE trial): statistical analysis plan for a recursive two-stage group sequential randomized controlled trial. *Trials*. 2020;21(1):8. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31900204.

6. Interferon beta-1b (BETASERON) [prescribing information]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/103471s5195lbl.pdf. Accessed: April 8, 2020.

7. Interferon beta-1a (REBIF) [prescribing information].Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/103780s5204lbl.pdf. Accessed: April 8, 2020.

8. Sarilumab (KEVZARA) [prescribing information]. Food and Drug Administration. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761037s001lbl.pdf. Accessed: April 8, 2020.

9. Regeneron and Sanofi provide update on U.S. Phase 2/3 adaptive-designed trial of KEVZARA® (sarilumab) in hospitalized COVID-19 patients [press release]. 2020.

10. SYLVANT (siltuximab) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125496s018lbl.pdf. Accessed: May 5, 2020.

11. Tocilizumab (ACTEMRA) [prescribing information]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125276s127,125472s040lbl.pdf. Accessed: April 8, 2020.

12. Baricitinib (OLUMIANT) [prescribing information]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/207924s001lbl.pdf. Accessed: April 8, 2020.

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]

References

1. Han H, Yang L, Liu R, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. *Clin Chem Lab Med*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32172226.

2. Driggin E, Madhavan MV, Bikdeli B, et al. Cardiovascular considerations for patients, health care workers, and health systems during the coronavirus disease 2019 (COVID-19) pandemic. *J Am Coll Cardiol*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32201335.

3. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32109013.

4. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost*. 2020;18(5):1094-1099. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32220112.

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

6. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients in severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med*. 2020:[Preprint]. Available at: https://www.esicm.org/wp-content/uploads/2020/04/863_author_proof.pdf.

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

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

9. Goyal P, Choi JJ, Pinheiro LC, et al. Clinical characteristics of COVID-19 in New York City. *N Engl J Med*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32302078.

10. Paranjpe I, Fuster V, Lala A, et al. Association of treatment dose anticoagulation with in-hospital survival

among hospitalized patients with COVID-19. *Journal of the American College of Cardiology*. 2020. [In Press]. Available at: https://www.sciencedirect.com/science/article/pii/S0735109720352189?via%3Dihub.

11. Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost*. 2020;18(5):1023-1026. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32338827.

12. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up. *J Am Coll Cardiol*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32311448.

13. American Society of Hematology. COVID-19 and VTE/anticoagulation: frequently asked questions. 2020. Available at: https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation. Accessed May 8, 2020.

14. Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. *Acta Paediatr*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32202343.

15. Iba T, Nisio MD, Levy JH, Kitamura N, Thachil J. New criteria for sepsis-induced coagulopathy (SIC) following the revised sepsis definition: a retrospective analysis of a nationwide survey. *BMJ Open*. 2017;7(9):e017046. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28963294.

16. Spyropoulos AC, Lipardi C, Xu J, et al. Modified IMPROVE VTE Risk score and elevated D-dimer identify a high venous thromboembolism risk in acutely ill medical population for extended thromboprophylaxis. *TH Open*. 2020;4(1):e59-e65. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32190813.

17. Cohen AT, Harrington RA, Goldhaber SZ, et al. Extended thromboprophylaxis with betrixaban in acutely ill medical patients. *N Engl J Med*. 2016;375(6):534-544. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27232649.

18. Bates SM, Rajasekhar A, Middeldorp S, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy. *Blood Adv*. 2018;2(22):3317-3359. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30482767.

19. ACOG Practice Bulletin No. 196 summary: thromboembolism in pregnancy. Obstet Gynecol. 2018;132(1):243-248. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29939933.

20. Wang M, Lu S, Li S, Shen F. Reference intervals of D-dimer during the pregnancy and puerperium period on the STA-R evolution coagulation analyzer. *Clin Chim Acta*. 2013;425:176-180. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23954836.

21. Reger B, Peterfalvi A, Litter I, et al. Challenges in the evaluation of D-dimer and fibrinogen levels in pregnant women. *Thromb Res*. 2013;131(4):e183-187. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23481480.

22. Hu W, Wang Y, Li J, et al. The predictive value of D-dimer test for venous thromboembolism during puerperium: a prospective cohort study. *Clin Appl Thromb Hemost*. 2020;26:1076029620901786. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32090610.

Considerations for Certain Concomitant Medications in Patients with COVID-19

(Last updated April 21, 2020)

Summary Recommendations

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

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

Corticosteroids

For Critically Ill Patients with COVID-19:

- The Panel **recommends against** the routine use of systemic corticosteroids for the treatment of mechanically ventilated patients with COVID-19 without acute respiratory distress syndrome (ARDS) **(AIII)**.
- For mechanically ventilated patients with ARDS, there is insufficient evidence to recommend for or against the use of systemic corticosteroids **(CI)**.
- For adults with COVID-19 and refractory shock, the Panel recommends using low-dose corticosteroid therapy (i.e., shock reversal) over no corticosteroids **(BII)**.

For Hospitalized, Non-Critically Ill Patients with COVID-19:

- The Panel **recommends against** the routine use of systemic corticosteroids for the treatment of COVID-19 in hospitalized patients, unless they are in the intensive care unit **(AIII)**.

For Patients on Chronic Corticosteroids:

- Oral corticosteroid therapy 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 used daily for patients with asthma and chronic obstructive pulmonary disease for control of airway inflammation should not be discontinued in patients with COVID-19 **(AIII)**.

Pregnancy Considerations:

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

HMG-CoA Reductase Inhibitors (Statins):

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

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs):

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

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

Recommendations:

- Persons with COVID-19 who are prescribed angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) for cardiovascular disease (or other indications) should continue these medications **(AIII)**.

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of ACE inhibitors or ARBs for the treatment of COVID-19 outside of the setting of a clinical trial **(AIII)**.

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

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

Corticosteroids

Systemic corticosteroids can affect the pathogenesis of viral infections in various ways. In outbreaks of other novel coronavirus infections[4,5] (i.e., Middle East respiratory syndrome [MERS] and severe acute respiratory syndrome [SARS]), corticosteroid therapy was associated with delayed virus clearance. In severe pneumonia caused by influenza, corticosteroid therapy may worsen clinical outcomes, including secondary bacterial infection and mortality.[6] Conversely, the potent anti-inflammatory effects of corticosteroids are proposed to have a potential therapeutic role in suppressing cytokine-related lung injury.[7] Data on the use of corticosteroids in COVID-19 are limited. The recommendations for use of corticosteroids in patients with COVID-19 depend on the severity of illness, indication, and underlying medical conditions and should be considered on a case-by-case basis.

Critically Ill Patients

For more information, see Care of Critically Ill Patients with COVID-19.

Recommendations:

- The Panel **recommends against** the routine use of systemic corticosteroids for the treatment of mechanically ventilated patients with COVID-19 without acute respiratory distress syndrome (ARDS) **(AIII).**

- For mechanically ventilated patients with ARDS, there is insufficient evidence to recommend for or against the use of corticosteroids **(CI)**.

- For adults with COVID-19 and refractory shock, the Panel recommends using low-dose corticosteroid therapy (i.e., shock reversal) over no corticosteroids **(BII)**.

Hospitalized, Non-Critically Ill Patients

Recommendation:

- The Panel **recommends against** the routine use of systemic corticosteroids for the treatment of

COVID-19 in hospitalized patients, unless they are in the intensive care unit **(AIII)**.

Guidelines outside of the United States have proposed the use of low-dose, short-course corticosteroids in patients with progressive deterioration of oxygenation or elevated inflammatory markers.[8,9] Epidemiologic studies from China describe that a short course (median 5 to 7 days) of methylprednisolone has been used. Other retrospective studies and case series describe that methylprednisolone may be associated with improved symptom resolution and mortality. These results should be interpreted with caution, considering the limitations of uncontrolled study designs, use of a small sample size, subset analysis, and lack of detailed information on the dose and timing of methylprednisolone.[10-12] The decision to use corticosteroids in patients with early signs of cytokine storm should be balanced with the known adverse effects.[13]

Patients on Chronic Systemic Corticosteroid Therapy

Recommendation:

- Oral corticosteroid therapy used prior to COVID-19 diagnosis for another underlying condition (e.g., primary or secondary adrenal insufficiency, rheumatological diseases) should not be discontinued **(AIII)**.[14] On a case-by-case basis, supplemental or stress-dose steroids may be indicated **(AIII)**.

Patients on Inhaled Corticosteroids

Recommendation:

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

Pregnancy Considerations

The antenatal corticosteroids betamethasone and dexamethasone are known to cross the placenta and therefore are generally reserved for when administration is required for fetal benefits **(BIII)**. Other systemic corticosteroids do not cross the placenta, and pregnancy is not a reason to restrict their use if otherwise indicated.[15]

The American College of Obstetricians and Gynecologists suggests the following modifications regarding the use of antenatal corticosteroids for fetal benefit for patients with suspected or confirmed COVID-19:[16]

- *Before 37 0/7 Weeks of Gestation:* For pregnant patients with suspected or conformed COVID-19 between 24 0/7 weeks and 33 6/7 weeks of gestation who are at risk of preterm birth within 7 days, antenatal corticosteroids should continue to be offered as recommended. Modifications to care for these patients may be individualized, weighing the neonatal benefits with the risks of potential harm to the pregnant patient.

- *Between 34 0/7 Weeks and 36 6/7 Weeks of Gestation (Late Preterm):* The benefits of antenatal corticosteroids in the late preterm period are less well established. Weighing this against any potential harm to the pregnant patient, antenatal corticosteroids should not be offered to pregnant patients with suspected or confirmed COVID-19 between 34 0/7 weeks and 36 6/7 weeks of gestation who are at risk of preterm birth within 7 days. Modifications to care for these patients may be individualized, weighing the neonatal benefits of antenatal corticosteroid use with the risks of potential harm to the pregnant patient.

HMG-CoA Reductase Inhibitors (Statins)

Recommendations:

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

HMG-CoA reductase inhibitors, or statins, affect ACE2 as part of their function in reducing endothelial dysfunction. It has been proposed that these agents have a potential role in managing patients with severe COVID-19.[17] Observational studies have reported that statin therapy may reduce cardiovascular morbidity in patients admitted with other respiratory infections, such as influenza and bacterial pneumonia.

Nonsteroidal Anti-Inflammatory Drugs

Recommendations:

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

In mid-March 2020, news agencies promoted reports that anti-inflammatory drugs may worsen COVID-19. It has been proposed that NSAIDs like ibuprofen can increase the expression of ACE2[1] and inhibit antibody production.[18] 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.[19]

References

1. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med*. 2020;8(4):e21. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32171062.

2. Patel AB, Verma A. COVID-19 and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: what is the evidence? *JAMA*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32208485.

3. American College of Cardiology. HFSA/ACC/AHA statement addresses concerns re: using RAAS antagonists in COVID-19. 2020. Available at: https://www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statement-addresses-concerns-re-using-raas-antagonists-in-covid-19.

4. Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid therapy for critically ill patients with Middle East respiratory syndrome. *Am J Respir Crit Care Med*. 2018;197(6):757-767. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29161116.

5. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Med*. 2006;3(9):e343. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16968120.

6. Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, Lim WS. Corticosteroids as adjunctive therapy in the treatment of influenza. *Cochrane Database Syst Rev*. 2016;3:CD010406. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26950335.

7. Siddiqi HK, Mehra MR. COVID-19 Illness in Native and Immunosuppressed States: A Clinical-Therapeutic Staging Proposal. *The Journal of Heart and Lung Transplantation*. 2020. [In Press]. Available at: https://www.jhltonline.org/article/S1053-2498(20)31473-X/fulltext.

8. China National Health Commission. Chinese clinical guidance for COVID-19 pneumonia diagnosis and treatment. Seventh Edition. 2020. Available at: http://kjfy.meetingchina.org/msite/news/show/cn/3337.html.

9. Shang L, Zhao J, Hu Y, Du R, Cao B. On the use of corticosteroids for 2019-nCoV pneumonia. *Lancet*. 2020;395(10225):683-684. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32122468.

10. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32167524.

11. Wang Y, Jiang W, He Q, et al. Early, low-dose and short-term application of corticosteroid treatment in patients with severe COVID-19 pneumonia: single-center experience from Wuhan, China. 2020. [Preprint]. Available at: https://www.medrxiv.org/content/10.1101/2020.03.06.20032342v1.

12. Sun F, Kou H, Wang S, et al. Medication patterns and disease progression among 165 patients with coronavirus disease 2019 (COVID-19) in Wuhan, China: a single-centered, retrospective, observational study. *Preprints with the Lancet*. 2020. [Preprint]. Available at: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3551323.

13. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet*. 2020;395(10223):473-475. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32043983.

14. Kaiser UB, Mirmira RG, Stewart PM. Our response to COVID-19 as endocrinologists and diabetologists. J *Clin Endocrinol Metab*. 2020;105(5). Available at: https://www.ncbi.nlm.nih.gov/pubmed/32232480.

15. Resnik R, Lockwood C, Moore T, Greene M, Copel J, Silver R. *Creasy and Resnik's Maternal-Fetal Medicine: Principles and Practice*. 8th Edition. 2018. Elsevier.

16. The American College of Obstetricians and Gynecologists. Practice advisory: novel coronavirus 2019 (COVID-19). Available at: https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2020/03/novel-coronavirus-2019.

17. Fedson DS, Opal SM, Rordam OM. Hiding in plain sight: an approach to treating patients with severe COVID-19 infection. *mBio*. 2020;11(2). Available at: https://www.ncbi.nlm.nih.gov/pubmed/32198163.

18. Bancos S, Bernard MP, Topham DJ, Phipps RP. Ibuprofen and other widely used non-steroidal anti-inflammatory drugs inhibit antibody production in human cells. *Cell Immunol*. 2009;258(1):18-28. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19345936.

19. Food and Drug Administration. FDA advises patients on use of non-steroidal anti-inflammatory drugs (NSAIDs) for COVID-19. 2020. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-patients-use-non-steroidal-anti-inflammatory-drugs-nsaids-covid-19. Accessed April 8, 2020.

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

(Last updated May 12, 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
Members	
Judith Aberg, MD	Icahn School of Medicine at Mount Sinai, New York, NY
Adaora Adimora, MD, MPH	University of North Carolina School of Medicine, Chapel Hill, NC
Jason Baker, MD, MS	Hennepin Healthcare/University of Minnesota, Minneapolis, MN
Lisa Baumann Kreuziger, MD, MS	Versiti/Medical College of Wisconsin, Milwaukee, WI
Roger Bedimo, MD, MS	University of Texas Southwestern/Veterans Affairs North Texas Health Care System, Dallas, TX
Pamela S. Belperio, PharmD	Department of Veterans Affairs, Los Angeles, CA
Stephen V. Cantrill, MD	Denver Health, Denver, CO
Ann C. Collier, MD	University of Washington School of Medicine, Seattle, WA
Craig Coopersmith, MD	Emory University School of Medicine, Atlanta, GA
Eric Daar, MD	Harbor-UCLA Medical Center, Torrance, CA
Susan L. Davis, PharmD	Wayne State University School of Pharmacy, Detroit, MI
Amy L. Dzierba, PharmD	New York-Presbyterian Hospital, New York, NY
Laura Evans, MD, MSc	University of Washington, Seattle, WA
Rajesh Gandhi, MD	Massachusetts General Hospital/Harvard Medical School, Boston, MA
David V. Glidden, PhD	University of California San Francisco, San Francisco, CA
Birgit Grund, PhD	University of Minnesota, Minneapolis, MN
Erica J. Hardy, MD, MMSc	Warren Alpert Medical School, Brown University, Providence, RI
Brenna L. Hughes, MD, MSc	Duke University School of Medicine, Durham, NC
Steven Johnson, MD	University of Colorado School of Medicine, Aurora, CO
Marla J. Keller, MD	Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY
Arthur Kim, MD	Massachusetts General Hospital and Harvard Medical School, Boston, MA
Jeffrey L. Lennox, MD	Emory University School of Medicine, Atlanta, GA
Mitchell M. Levy, MD	Warren Alpert Medical School, 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
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
Pablo Tebas, MD	University of Pennsylvania, Philadelphia, PA

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

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

(Last updated May 12, 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, DTMH, 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
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