Introduction

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 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

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).

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.

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Persons at Risk for Infection with SARS-CoV-2

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

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 Therapeutic Options for COVID-19 Currently Under Investigation. 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 (SaO_2) >93% on room air at sea level.
- *Severe Illness*: Individuals who have respiratory frequency >30 breaths per minute, SaO_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 immunomodulatory therapy in patients with 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 Therapeutic Options for COVID-19 Currently Under Investigation section and Tables 2a and 3a of these guidelines to review the available clinical data regarding 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 there is no evidence of bacterial infection, de-escalate or stop antibiotics.

Evaluation should include pulmonary imagining (chest x-ray, ultrasound, or if indicated, CT) and ECG, if indicated. Laboratory evaluation includes 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 Therapeutic Options for COVID-19 Currently Under Investigation section 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 acknowledges the work of the SSC COVID-19 Guidelines Panel.

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

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 Therapeutic Options for COVID-19 Currently Under Investigation section and Tables 2a and 3a of these guidelines to review the available clinical data regarding drugs being evaluated for treatment of this disease.

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Special Considerations in Pregnancy and Post-Delivery

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 risk of vertical transmission of SARS-CoV-2 via the transplacental route.[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 Therapeutic Options for COVID-19 Currently Under Investigation 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, CDC recommends temporarily separating newborn infants from mothers who are persons under investigation (PUI) for SARS-CoV-2 or who have COVID-19 because of concern for transmission of SARS-CoV-2 to the infant via respiratory droplets.
- ACOG supports breastfeeding for infants. They recommend that, for women who are PUI or confirmed to have SARS-CoV-2 infection, the decision about whether and how to start or continue breastfeeding be made by the mother in coordination with her family and health care practitioners.[11]
- CDC has developed interim guidance on breastfeeding, recommending that women who intend to breastfeed and who are temporarily separated from their infants express their breastmilk, ideally from a dedicated pump, practice good hand hygiene before and after pumping, and consider having a healthy person feed the infant.
- CDC advises that women with COVID-19 who choose to room-in with their infants and feed them at the breast should practice good hand hygiene and wear a facemask to prevent transmission of the virus to the infant via respiratory droplets during breastfeeding.[1] SARS-CoV-2 has not been isolated from breast milk.[5]

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Special Considerations in Children

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 are insufficient data to recommend for or against the use of specific antivirals or immunomodulatory agents for the treatment of COVID-19 in pediatric patients (AIII). 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 Therapeutic Options for COVID-19 Currently Under Investigation to review special considerations for use of these drugs in children and refer toTable 2b for dosing recommendations in children.

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Care of Critically Ill Patients with COVID-19

Summary Recommendations

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 (N-95 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).
- The Panel recommends using dobutamine in patients who show evidence of persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents (BII).

Ventilatory Support:

- For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy, the Panel recommends high-flow nasal cannula (HFNC) oxygen over noninvasive positive pressure ventilation (NIPPV) (BI).
- In the absence of an indication for endotracheal intubation, the Panel recommends a closely monitored trial of NIPPV for adults with COVID-19 and acute hypoxemic respiratory failure for whom HFNC is not available (BIII).
- For adults with COVID-19 who are receiving supplemental oxygen, the Panel recommends close monitoring for worsening of respiratory status and recommends early intubation 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 antiviral or 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).

General Considerations

Co-Morbid Conditions

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

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

Bacterial Superinfection of COVID-19-Associated Pneumonia

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

Septic Shock and Cytokine Storm Due to COVID-19

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

COVID-19-Induced Cardiac Dysfunction, Including Myocarditis

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

Renal and Hepatic Dysfunction Due to COVID-19

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

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

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

chloroquine or hydroxychloroquine is a potential problem for patients with underlying heart disease and/or those who concurrently use drugs that prolong the QTc interval (e.g., azithromycin, quinolones).

Other Intensive Care Unit-Related Complications

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

Goals of Care

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

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

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Infection Control

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 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 nonventilated COVID-19 patients, the Panel recommends wearing surgical masks, rather than respirator masks, along with other PPE (BIII).
- For health care workers who are performing nonaerosol-generating procedures on mechanically ventilated (closed circuit) patients with COVID-19, the Panel recommends wearing surgical mask along with other PPE (BIII).

Rationale

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).[5, 6] 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.[7]

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.[8, 9] Thus, the Panel recommends that the health care operator with the most experience and skill in airway management be the first to attempt intubation. The close facial proximity of direct laryngoscopy can expose health care providers to higher concentrations of viral aerosols. Finally, it is important to avoid having unnecessary staff in the room.

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Laboratory Diagnosis

Recommendations:

- For intubated and mechanically ventilated adults who are suspected to have coronavirus disease 2019 (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

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

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

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Hemodynamics

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.
- The Panel recommends using dopamine as an alternative vasopressor agent to norepinephrine only in certain patients (e.g., patients with low risk of tachyarrhythmias and absolute or relative bradycardia) (BII).
- The Panel recommends against using low-dose dopamine for renal protection (BII).
- The Panel recommends using dobutamine in patients who show evidence of persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents (BII).
- The Panel recommends that all patients who require vasopressors have an arterial catheter placed as soon as practical, if resources are available (BIII).
- For adults with COVID-19 and refractory shock, the Panel recommends using low-dose corticosteroid therapy (“shock-reversal”) over no corticosteroid (BII).
    - A typical corticosteroid regimen in septic shock is intravenous hydrocortisone 200 mg per day administered either as an infusion or intermittent doses. The duration of hydrocortisone therapy is usually a clinical decision.

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Oxygenation and Ventilation

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 COVID-19 Treatment Guidelines Panel (the Panel) recommends close monitoring for worsening respiratory status and recommends early intubation 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).

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Pharmacologic Interventions

Recommendations:

- There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against any antiviral or 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.

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Extracorporeal Membrane Oxygenation

Recommendation:

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

Rationale

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

ECMO is used by some experts, when available, for patients with refractory hypoxemia despite optimization of ventilation strategies and adjunctive therapies. Ideally, clinicians who are interested in using ECMO should either try to enter their patient into clinical trials or clinical registries so that more informative data can be obtained. The following resources provide more information on the use of ECMO in patients with COVID-19:

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

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Therapeutic Options for COVID-19 Currently Under Investigation

Summary Recommendations

At present, no drug has been proven to be safe and effective for treating COVID-19. There are no Food and Drug Administration (FDA)-approved drugs specifically to treat patients with 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 optimal 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:

- There are insufficient clinical data to recommend either for or against using chloroquine or hydroxychloroquine for the treatment of COVID-19 (AIII).
  - If chloroquine or hydroxychloroquine is used, clinicians should monitor the patient for adverse effects, especially prolonged QTc interval (AIII).
- There are insufficient clinical data to recommend either for or against using the investigational antiviral drug remdesivir for the treatment of COVID-19 (AIII).
  - Remdesivir as a treatment for COVID-19 is currently being investigated in clinical trials and is also available through expanded access and compassionate use mechanisms for certain patient populations.
- Except in the context of a clinical trial, the COVID-19 Treatment Guidelines Panel (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.

Host Modifiers/Immune-Based Therapy:

- There are insufficient clinical data to recommend either for or against the use of convalescent plasma or hyperimmune immunoglobulin for the treatment of COVID-19 (AIII).
- There are insufficient clinical data to recommend either for or against the use of the following agents for the treatment of COVID-19 (AIII):
  - Interleukin-6 inhibitors (e.g., sarilumab, siltuximab, tocilizumab)
  - Interleukin-1 inhibitors (e.g., anakinra)
- Except in the context of a clinical trial, the Panel recommends against the use of other immunomodulators, such as:
  - Interferons (AIII), because of 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.

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

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

Chloroquine or Hydroxychloroquine

Recommendation:

- There are insufficient clinical data to recommend either for or against using chloroquine or hydroxychloroquine for the treatment of COVID-19 (AIII).
  - When chloroquine or hydroxychloroquine is used, clinicians should monitor the patient for adverse effects (AEs), especially prolonged QTc interval (AIII).

Rationale for Recommendation:

Chloroquine and hydroxychloroquine have been used in small randomized trials[1] and in some case series 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.

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 less toxicity (including less propensity to prolong the QTc interval) and fewer drug-drug interactions than chloroquine.

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

- Both chloroquine and hydroxychloroquine increase the endosomal pH, inhibiting fusion of the SARS-CoV-2 and the host cell membrane.[2]
- Chloroquine inhibits glycosylation of the cellular angiotensin-converting enzyme 2 (ACE2) receptor, which may interfere with binding of SARS-CoV to the cell receptor.[3]
- *In vitro*, both drugs may block the transport of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from early endosomes to endolysosomes, which may be required for release of the viral genome.[4]
- Several studies have demonstrated *in vitro* activity of chloroquine against SARS-CoV.[3,5]
- Both drugs have immunomodulatory effects.

Clinical Data in 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; data on use of the drugs in patients with severe and critical COVID-19 are very limited. The clinical data are summarized below.

Chloroquine

Study Description:

In a small randomized controlled trial in China, 22 hospitalized patients with COVID-19 (none critically ill) were randomized to chloroquine 500 mg orally twice daily or lopinavir 400 mg/ritonavir 100 mg twice daily for 10 days. Patients with a history of heart disease (chronic disease and history of arrhythmia), kidney, liver, or hematologic diseases were excluded from participation. 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. Patients had good peripheral capillary oxygen saturation (SpO_2) at baseline (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 negative SARS-CoV-2 PCR. 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 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 drugs 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 with chronic co-morbidities and critically ill patients were excluded from the study.

Hydroxychloroquine

Study Description:

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 hydroxychloroquine 200 twice daily for 5 days plus standard treatment or to standard treatment only.[6] 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).
- 13% of the control patients and none of the hydroxychloroquine-treated patients experienced progression of illness.
- 80.6% of hydroxychloroquine-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 2 (6.4%) hydroxychloroquine-treated patients; none occurred among the control patients.

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 co-morbidities (e.g., hypertension [HTN], 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.

Study Description:

A pilot trial in China randomized 30 patients with COVID-19 to hydroxychloroquine 400 mg once a day for 5 days or conventional treatment.

Results:

- The trial demonstrated no difference in viral clearance of nasopharyngeal (NP) swabs at Day 7 between the hydroxychloroquine arm (86.7%) and the control arm (93.3%).[7]
- One patient in the hydroxychloroquine arm progressed to severe pneumonia. At follow-up, all patients showed clinical improvement.

Study Description:

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 3 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).[8]

Results:

- Six patients in the hydroxychloroquine group were excluded from the analysis for the following reasons:
  - One died
  - Three were transferred to the intensive care unit (ICU)
  - One stopped the study drug due to nausea
  - One withdrew from the study
- Six patients also received azithromycin.
- By Day 6, 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%) who received only hydroxychloroquine and 6 of 6 (100%) 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 small sample size of the series.
  - 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.

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)[9] should be used only if necessary. Consider using doxycycline rather than azithromycin as empiric therapy for atypical pneumonia.
  - Baseline and follow-up electrocardiogram (ECG) are recommended when there are potential drug interactions with concomitant medications (e.g., azithromycin) or underlying cardiac diseases.[10]
  - 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).[11]

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 Food and Drug Administration (FDA)-approved 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 COVID-19 patients who weigh ≥50 kg and for whom a clinical trial is not available, or participation is not feasible.

Hydroxychloroquine plus Azithromycin

Recommendation:

- The COVID-19 Treatment Guidelines Panel (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 was associated with QTc prolongation in patients with COVID-19.

Clinical Data in COVID-19

Study Description:

In a case series of 80 hospitalized patients with COVID-19 (including six patients from a previous study),[8] patients were treated with hydroxychloroquine sulfate 200 mg three times daily for 3 to 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 4.9 ± 3.6 days. Outcomes evaluated included the need for oxygen therapy or ICU transfer after ≥3 days of therapy, NP PCR, SARS-CoV-2 culture, and length of hospitalization.[12,13]

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:

- 40 of 60 (66.7%) patients tested on Day 6 had negative NP PCR.
- All patients tested had negative PCRs by Days 12 through14.
- Culture positivity decreased over time among the small number of patients for whom cultures were obtained.

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 criteria for selection of cases was not reported.
- Data for PCR and culture results were missing.
- The definition of "discharge" varied and was unclear.
- The lack of complete or longer-term follow-up.

Study Description:

A prospective case series from France of 11 consecutive hospitalized patients with COVID-19 (eight with significant co-morbid conditions: obesity in two; solid cancer in three; hematological cancer in two; HIV-infection in one). Ten of 11 patients were receiving supplemental oxygen upon treatment initiation.[13] All patients were treated with hydroxychloroquine 600 mg once daily for 10 days and azithromycin 500 mg for 1 day followed by 250 mg once daily for 4 days.

Results:

- Within 5 days, the condition of three patients worsened, including one patient who died and two patients who were transferred to the ICU.
- AEs: 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 (repeat testing not done in the patient who died).

Study Description:

A case series in the United States reported changes in QTc interval in 84 patients with COVID-19 who received the combination of hydroxychloroquine and azithromycin.[14]

Results:

- 84 patients, 74% male, mean age 63 ± 15 years, 65% had HTN, baseline serum creatinine 1.4 mg/dL, 13% required vasopressors, 11% had coronary artery disease.
- Concomitant drugs that may prolong QTc interval: 11% on neuropsychiatric drugs and 8% received levofloxacin, lopinavir/ritonavir or tacrolimus.
- Four patients died, without arrhythmia.
- Mean baseline QTc was 435 ± 24 ms, mean maximum QTc was 463 ± 35 ms.
- Mean time to maximum QTc was 3.6 ±1.6 days, ECG follow-up was done for a mean of 4.3 days.
- 11% of patients developed QTc >500 ms; the QTc increased by 40 to 60 ms and >60 ms in 18% and 12% of patients, respectively.
- Baseline QTc was not a predictor of subsequent QTc increase during therapy.
- In multivariate analysis, acute kidney injury (in five patients) was a significant predictor of severe QTc prolongation (odds ratio [OR] 19.45: 95% CI, 2.06–183.88, $P = 0.01$).

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 in development in the United States and internationally. Please check *ClinicalTrials.gov* for the latest information.

Lopinavir/Ritonavir and Other HIV Protease Inhibitors

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 do not support their therapeutic use for COVID-19. Also, lopinavir/ritonavir was studied in a small randomized controlled trial in patients with COVID-19 with negative results (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.[15] The enzymes responsible for this cleavage are two proteases, 3-chymotrypsin-like protease (3CLpro) and papain-like protease (PLpro).
- Lopinavir/ritonavir is an inhibitor of SARS-CoV 3CLpro *in vitro*, and this protease appears highly conserved in SARS-CoV-2.[16,17]
- Although lopinavir/ritonavir has *in vitro* activity against SARS-CoV, it is thought to have a poor selectivity index, indicating that higher than tolerable levels of the drug might be required to achieve meaningful inhibition *in vivo*.[18]
- Lopinavir is excreted in the gastrointestinal (GI) tract, and thus coronavirus-infected enterocytes might be exposed to higher concentrations of the drug.[19]

Clinical Data in COVID-19:

Study Description:

- In a Chinese cohort of 55 pre-symptomatic patients identified early in the course of the infection (i.e., tested RT-PCR positive after a family member or close contact was found to have COVID-19), all of whom were given lopinavir/ritonavir for 7 days; all recovered and none required ICU admission.[20]

Study Description:

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.[21]

Results:

- There was a lower, but not statistically significant, mortality rate (lopinavir/ritonavir 19.2%, on SOC 25.0%) and shorter ICU stay 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 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.

Study Description:

In a trial of 44 hospitalized patients with mild-to-moderate COVID-19, 21 patients were randomized to lopinavir/ritonavir, 16 patients to the broad-spectrum antiviral Arbidol (available in Russia), and seven patients to SOC.[22]

Results:

- The time to a negative SARS-CoV-2 nucleic acid pharyngeal swab was not shorter for patients receiving lopinavir/ritonavir (8.5 days [IQR: 3, 13]) than for those receiving SOC (4 days [IQR: 3, 10.5]).
- Progression to severe/critical status occurred among eight (38%) patients receiving lopinavir/ritonavir and one patient (14%) on SOC.

Study Description:

A small randomized study in China compared lopinavir/ritonavir to chloroquine. Please refer to the chloroquine section for the study description.[23]

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 SARS-CoV-2 infection 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.
- 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.[24]

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.

Remdesivir

Recommendation:

- There are insufficient clinical data to recommend either for or against the use of the investigational antiviral agent remdesivir for the treatment of COVID-19 (AIII).

Rationale for Recommendation:

Remdesivir is an investigational antiviral drug. Clinical trials of remdesivir for treatment of COVID-19 are underway or in development, but trial data is not yet available.

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 SARS-CoV-2,[2] and *in vitro* and *in vivo* activity (based on animal studies) against SARS-CoV and MERS-CoV.[25-27] 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.[25] 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.[27] When given 12 hours after MERS-CoV infection to rhesus macaques, remdesivir reduced viral replication and the severity of lung disease compared to control animals.

Remdesivir is administered by intravenous infusion at 200 mg on Day 1 followed by 100 mg/day for up to 10 days; the drug is usually infused over 30 to 60 minutes.

Clinical Data to Date:

Only anecdotal data are available.

Clinical Trials:

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

In areas of the United States without access to clinical trials, remdesivir may be available through an expanded access program or compassionate use program for a subset of patients.

Monitoring, Adverse Effects, and Drug-Drug Interactions:

Remdesivir can cause GI symptoms (e.g., nausea, vomiting), elevated transaminases, and prothrombin time elevation (without change in international normalized ratio [INR]). Remdesivir is a CYP3A4, CYP2C8, and CYP2D6 substrate *in vitro*. 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.[28]

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

Considerations in Pregnancy:

- Remdesivir is available for pregnant women through a compassionate access program.
- 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.[29]

Considerations in Children:

- Currently, remdesivir is available for compassionate use for patients aged <18 years.
- In the same randomized controlled trial for the treatment of Ebola virus infection, 41 pediatric patients aged <7 days to <18 years received remdesivir.[29] The safety and clinical outcomes in children were not reported separately in the published results for the trial.

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

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date (Find clinical trials on)
Azithromycin Note: Studies on COVID-19 use azithromycin with hydroxychloroquine.	• 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]	Azithromycin 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.
Chloroquine	• Malaria • Extraintestinal 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]	In a small randomized controlled trial in China, 22 patients with COVID-19 who were hospitalized, but not critically ill, were randomized to receive chloroquine 500 mg PO twice daily or LPV/r 400 mg/100 mg twice daily for 10 days. Ten patients received chloroquine and 12 patients received LPV/r.[7] The chloroquine-treated patients had a shorter duration from symptom onset to initiation of treatment (2.5 days vs. 6.5 days; $P < 0.001$). Outcomes included SARS-CoV-2-negative PCR at Days 10 and 14, CT scan improvement at Days 10 and 14, and discharge at Day 14. The risk ratios of these outcome results crossed 1 and were not statistically significant between groups.

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date (Find clinical trials on)
Hydroxychloroquine	• Lupus erythematosus • Malaria • Rheumatoid arthritis[8]	• *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]	In a small randomized controlled trial in China, 62 hospitalized patients with "mild" COVID-19 pneumonia were randomized to receive HCQ 200 mg PO twice daily for 5 days versus standard treatment (which included O_2, antivirals, antibacterials, and immunoglobulin, with or without steroids).[7,9] Mean duration of fever and cough was 1 day shorter among HCQ-treated patients than among controls. Thirteen percent of control patients and none of the HCQ-treated patients experienced progression of illness; 80.6% of the HCQ-treated patients experienced either moderate or significant improvement in chest CT scan compared to 54.8% of controls. This study had a small sample size and a short follow-up period; in addition, "standard treatment" and progression of illness were not well defined, and the study did not report on the distribution of co-morbidities or specify whether the radiologists were blinded. A prospective trial randomized 30 patients with mild COVID-19 to receive HCQ 400 mg once daily for 5 days plus conventional treatment (100% of patients received interferon alfa, 80% received Arbidol [umifenovir], 2% received LPV/r) or conventional treatment alone. On Day 7, NP swab was negative in 86.7% of the HCQ group versus 93.3% of the control group ($P > 0.05$). One patient in the HCQ group progressed to severe pneumonia. In a case series of 42 patients with COVID-19, 26 patients received HCQ 200 mg three times daily for 10 days, and there were 16 control patients. Six patients who received HCQ were not included in the analysis due to death, ICU transfer, AEs, or withdrawal. Fourteen patients received HCQ alone; six patients received HCQ plus azithromycin. See Therapeutic Options for COVID-19 Currently Under Investigation for details on the significant methodological concerns for these data.
Hydroxychloroquine plus Azithromycin	See the Azithromycin plus Hydroxychloroquine section above.	See the Azithromycin plus Hydroxychloroquine section above.	In a single-center case series of 80 patients with generally mild COVID-19 who received HCQ 200 mg three times daily and azithromycin for ≥3 days and who had ≥6 days of data, 66% had negative PCR using NP swab by Day 6. See Therapeutic Options for COVID-19 Currently Under Investigation for details on the significant methodological concerns for these data. In a prospectively studied case series in France of 11 consecutive hospitalized patients with COVID-19, all were treated with HCQ 600 mg daily for 10 days and azithromycin 500 mg for 1 day followed by 250 mg once daily for 4 days. Within 5 days, three patients worsened, including one who died and two who were transferred to the ICU. HCQ was discontinued in one patient due to QTc prolongation. Qualitative PCR using NP swab remained positive at Days 5 and 6 after treatment initiation in 8 of 10 patients (repeat testing was not done in one patient because of death).[11] A case study that evaluated QTc before and after initiation of HCQ plus azithromycin in 84 patients noted that 11% of the patients had peak QTc >500 ms; 30% had their QTc interval increase by >30 ms from baseline; and peak QTc occurred at 3.6 ± 1.6 days after beginning treatment. Baseline QTc was not a predictor of QTc increase during therapy. Acute kidney injury was a strong predictor of severe QTc prolongation.[12]

Drug Name	FDA-Approved Indications	Preclinical Data/Mechanism of Action	Clinical Data to Date (Find clinical trials on)
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 against SARS-CoV-2 • Possible inhibition of SARS-CoV-2 protease 3CLpro[13]	In an open-label, randomized controlled trial, 199 participants with COVID-19 were randomized to receive LPV/r 400 mg/100 mg twice daily for 14 days or standard of care. Participants enrolled a median of 13 days after symptom onset. No difference in primary outcome (time to clinical improvement) was observed, and 28-day mortality was similar between groups. About 50% of participants in each group experienced AEs; 13.8% in the LPV/r group could not complete treatment due to AEs.[7] In an exploratory, randomized controlled trial of 44 participants with mild-moderate COVID-19, 21 participants were randomized to receive LPV/r, 16 to receive Arbidol (umifenovir), and seven participants were in the control group. No differences were observed in the primary outcome (time to conversion of SARS-CoV-2 nucleic acid from treatment initiation to Day 21) or in clinical measures (rates of antipyretic treatment, cough alleviation, improvement in chest CT scan, or deterioration rate). In the LPV/r group, five participants (23.8%) experienced AEs versus none in the Arbidol (umifenovir) group or control group.[14] See the Chloroquine section for a description of a randomized controlled trial that compared LPV/r to chloroquine.[7] Results from an unpublished study in China showed that DRV/c is not effective in the treatment of COVID-19.[15]
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[16] • Potent *in vitro* activity demonstrated in SARS-CoV-2-infected Vero E6 cells[17]	Single case report of a 35-year-old man with COVID-19 who progressed to pneumonia by Day 9, requiring supplemental oxygen. Remdesivir was started on Day 11 and improvement was observed by Day 12; the patient was afebrile and asymptomatic except for cough by Day 15.[18]

Key: ACE2 = angiotensin-converting enzyme 2; AE = adverse effect; DRV/c = darunavir/cobicistat; FDA = Food and Drug Administration; ICU = intensive care unit; IL = interleukin; IFN = interferon; HCQ = hydroxychloroquine; LPV/r = lopinavir/ritonavir; NP = nasopharyngeal; PCR = polymerase chain reaction; PO = orally; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; STI = sexually transmitted infection

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

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.

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

- The information in this table is derived from data on the use of these drugs for FDA-approved indications or from investigational trials, and it is supplemented with data from patients with COVID-19 where available.
- The effective dosing of these drugs for treatment of COVID-19 is unknown. Therefore, the doses listed below are primarily derived from FDA-approved indications or from clinical trials investigating therapies for COVID-19.
- There are limited or no data on dose modifications for patients with organ failure or those who require extracorporeal devices. Please refer to product labels, when available.
- Treatment-related AEs 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 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*.

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

Drug Name	Dosing Regimens *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials for COVID-19.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Azithromycin (When Used with Hydroxychloroquine in Reported Cases)	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 hydroxychloroquine and chloroquine)	The Panel recommends against use of HCQ plus azithromycin except in a clinical trial setting (AIII). A list of clinical trials is available here: Azithromycin
Chloroquine	Suggested Dose in EUA[a] for Adults/Adolescents Weighing ≥50 kg: • 1 gram PO one-time dose 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 if 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	• 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; chloroquine is not recommended in patients with G6PD deficiency. Consider using HCQ instead of chloroquine while awaiting G6PD results.	• Additive effect with other drugs that prolong the QTc interval (including azithromycin) or cause hypoglycemia • CYP2D6 inhibitor (moderate) • P-gp inhibitor	There are insufficient data for the Panel to recommend for or against the use of chloroquine (AIII). Available through EUA for hospitalized patients who cannot access chloroquine via clinical trials Dose-dependent toxicity A list of clinical trials is available here: Chloroquine
Hydroxychloroquine	Adults: • Various loading and maintenance doses have been reported in studies or in clinical care. Suggested Dose in EUA[a] for Hospitalized Adults/Adolescents Weighing ≥50 kg:	• Prolonged QTc interval, Torsades de Pointes, AV block, ventricular arrhythmia • Gastrointestinal effects (e.g., nausea, vomiting,	• CBC, hepatic panel, blood glucose, SCr, potassium, magnesium • Baseline ECG • Follow-up ECG if given with concomitant QTc prolonging drugs (e.g., azithromycin) or	• Additive effect with other drugs that prolong the QTc interval (including azithromycin) or cause hypoglycemia • CYP2D6 inhibitor (moderate) • P-gp inhibitor	There are insufficient data for the Panel to recommend for or against the use of hydroxychloroquine (AIII). The Panel recommends against the use of HCQ plus

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 for COVID-19.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Comments, and Links to Clinical Trials
	• 800 mg PO one-time dose 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 if 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 up to a total of duration of 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 up to a total duration of 5 days Neonates: • Dosing not established.	diarrhea, hepatitis) • Hypoglycemia • Myopathy • Anxiety, agitation, hallucinations, psychosis • Allergic reaction/rash	if underlying cardiac diseases		azithromycin except in a clinical trial setting (AIII). Panel's Recommendations, 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 for COVID-19.*	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 except in a clinical trial setting (AI). Liquid formulation commercially available. Crushing lopinavir/ritonavir tablets may result in significantly decreased drug exposure (AUC ↓ 45%).[1] Use with caution in patients with hepatic impairment. A list of clinical trials is available here: Lopinavir/Ritonavir
Remdesivir (GS-5734) *Investigational drug*	Adults: • 200 mg IV once on Day 1, followed by 100 mg IV every 24 hours • Duration of therapy varies per clinical trial (typically from 5–10 days) Children *<40 kg:* • 5 mg/kg IV loading dose on Day 1, followed by 2.5 mg/kg IV every 24 hours for 10 days *≥40 kg:* • 200 mg IV loading dose on Day 1, followed by 100 mg IV every 24 hours for 10 days	• Transient elevations in ALT or AST (Grade 1 or 2), typically after multiple days of therapy[2] • Mild, reversible PT prolongation without INR change or hepatic effects[2] • Potential for SBECD accumulation in moderate to severe renal impairment[2] • 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. It 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.	Insufficient data for the Panel to recommend for or against RDV use (AIII). Drug vehicle is SBECD, which has been associated with renal toxicity. Expanded access and compassionate use programs are available to certain patient populations.[3] A list of clinical trials is available here: Remdesivir

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 for COVID-19.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials

[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.

Key: AE = adverse effect; ALT = alanine transaminase; AST = aspartate aminotransferase; AUC = area under the curve; AV = atrioventricular; BID = twice daily; CBC = complete blood count; CYP = cytochrome P; ECG = electrocardiogram; 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; OATP = organic anion transporter polypeptide; P-gp = P-glycoprotein; PI = protease inhibitors; PMA = postmenstrual age; PO = orally; PT = prothrombin time; SCr = serum creatinine; RDV = remdesivir; SBECD = sulfobutyl ether β-cyclodextrin sodium; SNS = Strategic National Stockpile; UGT = uridine diphosphate glucuronyl transferase; ULN = upper limit of normal

Host Modifiers and Immune-Based Therapy Under Evaluation for Treatment of COVID-19

Several immune therapies directed at modifying the course of COVID-19 are currently under investigation or are 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 under evaluation for COVID-19, see Tables 3a and 3b.

Convalescent Plasma and Specific Immune Globulins

Recommendation:

- There are insufficient data to recommend either for or against the use of convalescent plasma or hyperimmune immunoglobulin for the treatment of COVID-19 (AIII).

Rationale for Recommendation:

Although convalescent plasma and hyperimmune immunoglobulin have been used for other viral infections, sufficient clinical data are lacking for COVID-19, and theoretical risks exist of antibody-dependent enhancement of infection and transfusion-associated acute lung injury (TRALI).

Rationale for Use in Patients with COVID-19:

Plasma donated from individuals who have recovered from COVID-19, which includes antibodies to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), may help suppress the virus and may modify the inflammatory response.[1-10] SARS-CoV-2 intravenous immune globulin (IVIG) is a concentrated antibody preparation derived from the plasma of people who have recovered from COVID-19.

Clinical Experience in Patients with Viral Infections:

- Data supporting the use of convalescent plasma for COVID-19 and severe acute respiratory syndrome (SARS) are limited to case reports and case series. There are no clinical data on the use of specific immune globulin or hyperimmune immunoglobulin in COVID-19, SARS, or Middle East respiratory syndrome (MERS).
- The use of convalescent plasma has been evaluated in other viral diseases, with some evidence of potential benefit. No such products are currently licensed by Food and Drug Administration (FDA).
- Several 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).
- Risks associated with plasma transfusion include antibody-mediated enhancement of infection, TRALI, transfusion-associated circulatory overload, and allergic transfusion reactions.[11] Rare complications include transmission of infectious diseases and red cell alloimmunization.
- Clinical trials to evaluate both convalescent plasma and SARS-CoV-2 IVIG for the treatment of COVID-19 are in development.
- FDA has provided guidance for the use of COVID-19 convalescent plasma under Emergency Investigational New Drug Application.
- 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 two 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.

Considerations in Pregnancy:

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

Considerations in Children:

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

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).[12] MAS is characterized by hyperinflammation and manifests as fever, elevated ferritin levels, and pulmonary involvement, with a spectrum of presentation that includes sHLH.[13] Viruses are known triggers of MAS/sHLH, and high ferritin levels are associated with both MAS and mortality in patients with COVID-19.[14,15] 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 (CAR-T) mediated cytokine release syndrome (CRS).[16] 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,[17] are reviewed below.

IL-1 Inhibitors (e.g., Anakinra)

Recommendation:

- There are insufficient data to recommend either for or against the use of 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-6 antagonist in patients with COVID-19.

Anakinra is a recombinant human IL-1 receptor antagonist (rhIL-1ra). It is approved to treat a variety of inflammatory conditions that range from RA to familial Mediterranean fever and is also used off-label for severe CAR-T-mediated CRS and MAS/sHLH.

Proposed Mechanism of Action and Rationale for Use:

Endogenous IL-1 is elevated in COVID-19 and other conditions, such as severe CAR-T-mediated CRS.

Clinical Data for COVID-19:

There are no published studies to date on the use of anakinra in COVID-19 infection or for other novel coronavirus infections (i.e., SARS, MERS).

Clinical Trials:

An open-label randomized trial underway in Italy is comparing IV-administered anakinra to IV-administered emapalumab (an interferon gamma [IFN**γ**]–blocking antibody) for the treatment of COVID-19.

Adverse Effects and Monitoring:

Anakinra was not associated with any significant safety concerns in trials of sepsis.[18-20] Increased rates of infection were reported with prolonged use in combination with tumor necrosis factor-alfa blockade, but not with short-term use.[21]

Considerations in Pregnancy:

Limited evidence on which to base a recommendation in pregnancy, but unintentional first trimester exposure is unlikely to be harmful.[22]

Considerations in Children:

- Anakinra has been used extensively in the treatment of severely ill children with complications of rheumatologic conditions, including MAS.
- Pediatric data for use of anakinra in acute respiratory distress syndrome (ARDS)/sepsis are limited.

Drug Availability:

Procurement of anakinra may be a challenge at some hospitals in the United States Anakinra is approved only in a subcutaneous (SQ) formulation.

IL-6 Inhibitors (Sarilumab, Siltuximab, Tocilizumab)

Recommendation:

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

Rationale for Recommendation:

There are no data from clinical trials on the use of IL-6 inhibitors in patients with COVID-19.

Rationale for Use of IL-6 Inhibition in 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.[23] 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, D-dimer, and ferritin, but typically not procalcitonin.[15,24,25]

Sarilumab

Sarilumab is a recombinant humanized anti-interleukin-6 receptor (IL-6R) monoclonal antibody that is FDA-approved for use in patients with RA. It is dosed subcutaneously (SQ) and is not approved for CRS. A placebo-controlled clinical trial is evaluating the use of an IV formulation administered as a single dose for COVID-19.

Clinical Data in COVID-19:

There are currently no data from randomized clinical trials or large observational cohorts describing the efficacy of sarilumab among patients with COVID-19.

Potential Adverse Effects and Monitoring:

Primary lab abnormalities reported with sarilumab treatment are transient/reversible elevations in liver enzymes that appear 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 FDA-approved but 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 that is FDA-approved for use in patients with Castleman's disease. Siltuximab prevents the binding of IL-6 to both soluble and membrane-bound IL-6R and thereby inhibits IL-6 signaling. Siltuximab is dosed as an IV infusion.

Clinical Data in COVID-19:

There are limited data describing the efficacy of siltuximab in patients with COVID-19.[26] There are also no data describing clinical experiences using siltuximab for patients with other novel coronavirus infections (i.e., SARS, MERS).

Potential Adverse Effects and Monitoring:

The primary 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:

It may be a challenge to procure siltuximab at some hospitals in the United States.

Tocilizumab

Tocilizumab is a recombinant humanized anti-IL-6R monoclonal antibody that is FDA-approved for use in patients with rheumatologic disorders and CRS-induced by CAR T-cell therapy. Tocilizumab can be dosed for IV or SQ injection. For CRS, the IV formulation should be used.[27]

Clinical Data for COVID-19:

- There are no data from randomized clinical trials or large observational cohort studies describing the efficacy of tocilizumab in patients with COVID-19.
- There are anecdotal reports of improved oxygenation in patients with COVID-19, systemic inflammation, and hypoxic respiratory failure who received tocilizumab.[28]

Potential Adverse Effects and Monitoring:

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

Considerations in Pregnancy:

There are insufficient data to determine whether there is a tocilizumab-associated risk for major birth defects and 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:

Tocilizumab is frequently used in CRS following CAR T-cell therapy,[29] and occasionally for MAS in children.[30] Pediatric data for its use in ARDS/sepsis are limited.

Drug Availability:

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

Clinical Trials:

See *ClinicalTrials.gov* for ongoing trials of tocilizumab for the treatment of COVID-19.

Other Immunomodulators

Interferons (Alpha, Beta)

Recommendation:

- 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:

Considered together, the absence of benefit when interferons were used in other coronavirus infections (i.e., MERS, SARS), the lack of clinical trial results in COVID-19, and the significant toxicities of interferons outweigh the potential for benefit.

Rationale for Use:

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

Clinical Data in COVID-19:

- Interferon-beta used alone and in combination with ribavirin in SARS and MERS has failed to show a significant positive effect on clinical outcomes.[31-35]
- In a retrospective observational analysis of 350 critically ill patients with MERS[32] 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 ARDS[36] found that, compared to placebo, IV interferon beta-1a had no benefit as measured by ventilator-free days over a 28-day period (median, 10.0 vs 8.5 days) or mortality (26.4% vs 23.0%).
- INF-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 and Monitoring:

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

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 pre-conception or during pregnancy and an increase risk of adverse birth outcomes (e.g., spontaneous abortion, congenital anomaly) and 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 (STAT) pathway. Baricitinib is FDA-approved to treat RA and can ameliorate the chronic inflammation seen in interferonopathies.[37-39]

Rationale for Use in 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.[40,41]

Clinical Data for COVID-19:

None reported to date.

Adverse Effects:

Side effects with prolonged use include upper respiratory infections (>10% of patients), increased 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 embryolethality in some species given baricitinib at very high doses, well above the recommended dose for humans.[42]
- The limited human data on the use of baricitinib are insufficient to evaluate the drug-associated risk for major birth defects or miscarriage.[42]

Corticosteroids

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

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

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)
Blood Products			
Convalescent Plasma	• Not approved by the FDA	• Plasma collected from patients who have recovered from COVID-19 may contain antibodies to neutralize and suppress SARS-CoV-2.	In a case series of five patients with COVID-19 and ARDS, patients were given two transfusions (400 mL total) of convalescent plasma, along with antiviral therapy and steroids. The transfusions were administered between 10 and 22 days after admission. Symptoms improved in all patients and no AEs were reported.[1] In a case series of 10 severely ill patients with COVID-19, patients were given antiviral therapy and one dose of convalescent plasma; six patients also received steroids. Transfusions were administered 10 to 20 days after symptom onset. Symptoms improved in all patients and no serious AEs were observed.[2] Use of convalescent plasma has been evaluated in other respiratory virus outbreaks, including H1N1 influenza, SARS, and MERS.
Intravenous Immunoglobulin (IVIG)	• Primary immune disorders • Thrombocytopenic purpura • Kawasaki disease • Measles • 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. • Suppression of inflammation • IVIG may have a role in limiting the inflammatory reaction associated with SARS-CoV-2 infection.	Several specific immune globulin products are approved by the FDA for prevention of post-transplant CMV disease (e.g., Cytogam) and post-exposure prophylaxis of varicella in high-risk individuals (e.g., VariZig). In small, observational studies of patients with COVID-19 in China, 20% of patients in Jiangsu province[3] and 27% in Wuhan[4] were treated with IVIG and with other therapies. Case reports have reported the use of IVIG plus steroids plus antimicrobial agents for the treatment of patients with COVID-19 with fulminant myocarditis[5] and acute myelitis,[6] and for a series of three patients with rapid deterioration.[7]
Interferons (INFs)			
Interferon-**α**	• IFN-**α**2b: Leukemia, melanoma, lymphoma, condylomata acuminata, Kaposi sarcoma, hepatitis B, hepatitis C • IFN-**α**1b is not available in the United States	• Elicits antiviral, antiproliferative, and immunomodulatory activities on numerous cell types[8-10]	No clinical data for COVID-19. For MERS:[11-14] • Retrospective studies with IFN-**α**2a, IFN-**α**2b, or IFN-**β**1a in combination with RBV showed no clear benefit. • RBV plus IFN-**α**2a survival rates: 30% to 100% in three small studies (n < 20)[15] • RBV plus IFN-**α**2a or IFN-**α**2b: No significant improvement in clinical outcome or survival at 28 days.[16] • RBV plus IFN-**β**1a SC: Retrospective analyses showed no significant effect on clinical outcome.[11] Inhaled IFN-**β**1a (SNG001):

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)
			• Phase 2 clinical trials showed improved lung function in asthma patients with respiratory infections[17]
Interferon-**β**	• Multiple sclerosis (IFN-**β**1a, **β**1b)	• Elicits antiviral, antiproliferative, and immunomodulatory activities on numerous cell types (T cell, B cell, and cytokine function)[8, 18] • Among IFN subtypes, IFN-**β**1b shows greatest *in vitro* inhibition of MERS-CoV.[13, 19] • *In vitro* activity against MERS-CoV in lung cells.[17]	
Interleukin (IL)-1 Inhibitor			
Anakinra	• Rheumatoid arthritis • Cryopyrin-associated periodic syndromes[20]	• Competitively inhibits IL-1 binding to the interleukin-1 type I receptor	No clinical data for COVID-19, SARS, or MERS
Interleukin (IL)-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[21]	• Human recombinant monoclonal antibody • L-6 receptor antagonist[22]	No clinical data for COVID-19, SARS, or MERS
Siltuximab	• Multicentric Castleman disease	• Human-mouse chimeric monoclonal antibody • IL-6 antagonist[23]	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)
Tocilizumab	• Cytokine release syndrome (induced by CAR T cell therapy) • Rheumatoid arthritis • Giant cell arteritis • Polyarticular juvenile idiopathic arthritis • Systemic juvenile idiopathic arthritis[24]	• Recombinant humanized monoclonal antibody • IL-6 receptor antagonist	There are anecdotal reports of use in patients with COVID-19 followed by improvements in oxygenation, systemic inflammation, and hypoxic respiratory failure.[25]
Jason (JAK) Kinase Inhibitor			
Baricitinib	• Rheumatoid arthritis[26]	• JAK inhibitor • Inhibition of kinases that regulate endocytosis (AAK1 and cyclin G-associated kinase) • Baricitinib is predicted to interfere with SARS-CoV-2 receptor-mediated endocytosis in lung AT2 alveolar epithelial cells.[27]	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).[27]

Key: AAK1 = AP2-associated protein kinase 1; ARDS = acute respiratory distress syndrome; AT2 = alveolar type 2; CAR = chimeric antigen receptor; CMV = cytomegalovirus; CRP = C-reactive protein; FDA = Food and Drug Administration; IL = interleukin; IV = intravenous; IVIG = intravenous immunoglobulin; JAK = Janus kinase inhibitor; MERS-CoV = Middle East respiratory syndrome coronavirus; RBV = ribavirin; SARS = severe acute respiratory syndrome; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

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

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.

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

- 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, and 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*.

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

Drug Name	Dosing Regimens *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials for COVID-19.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Blood Products					
Convalescent Plasma	250 mL to 300 mL up to three times over 5 days 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 infection, and hemolytic reactions	• 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 for the Panel to recommend for or against the use of convalescent plasma (AIII). FDA has provided guidance for the use of COVID-19 convalescent plasma under emergency IND. 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 this website for more information. A list of clinical trials is available here: Convalescent Plasma

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 for COVID-19.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Intravenous Immunoglobulin	Doses vary based on indication and formulation	• Thrombosis • 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.	There are insufficient data for the Panel to recommend for or against the use of IVIG (AIII). Titers against SARS-CoV-2 are likely to be low in the population presently. A list of clinical trials is available here: Intravenous Immunoglobulin
Interferons					

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 for COVID-19.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Interferon Alfa	Peginterferon alfa-2a 180 mcg SQ once weekly for 2 weeks for MERS[2, 3]	• Flu-like symptoms (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 RBV. 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

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 for COVID-19.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Interferon Beta	Interferon Beta-1a: • 44 mcg SQ three times weekly[3] for MERS • Duration unknown Interferon Beta-1b: • 0.25 mg SQ every 48 hours for MERS[5] • Duration unknown Interferon Beta-1a: • SNG001 (a formulation delivered by nebulization; not approved in the United States)	• Flu-like symptoms (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. Interferon Beta-1a Products: • Avonex, Rebif Interferon Beta-1b Products: • Betaseron, Extavia Interferon Beta-1a Product: • SNG001 (a formulation delivered by nebulization; not approved in United States) A list of clinical trials is available here: Interferon
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

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 for COVID-19.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Interleukin-6 Inhibitors					
Sarilumab[8]	Clinical Trial Dosing (See NCT04315298): • 400 mg IV vs. 200 mg IV vs. placebo (single dose) Note: The only FDA-approved sarilumab product is a SQ formulation.	• Neutropenia, thrombocytopenia • Gastrointestinal perforation • Hypersensitivity • Increased ALT and AST • Hepatitis B reactivation • Infusion reaction possible	• Hypersensitivity • Monitor for infusion reaction • Neutrophils, platelets, liver function	Elevated IL-6 may downregulate CYP enzymes; use of sarilumab may lead to increased metabolism of drugs that are CYP450 substrates. Effects on CYP450 may persist for weeks after therapy.	There are insufficient data for the Panel to recommend for or against the use of sarilumab (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[9] Dose and duration for COVID-19 unknown	• Infusion-related reaction • Gastrointestinal perforation • Neutropenia • Hypertension • Dizziness • Rash • Pruritus • Hyperuricemia	• Hypersensitivity • Monitor for infusion reaction • Neutrophils	Elevated IL-6 may downregulate CYP enzymes; use of siltuximab may lead to increased metabolism of drugs that are CYP450 substrates. Effects on CYP450 may persist for weeks after therapy.	There are insufficient data for the Panel to recommend for or against the use of siltuximab (AIII). May mask signs of acute inflammation (i.e., suppression of fever and CRP A list of clinical trials is available here: Siltuximab

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 for COVID-19.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel's Recommendations, Comments, and Links to Clinical Trials
Tocilizumab[10]	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 reaction • Hypersensitivity • Gastrointestinal perforation • Hepatotoxicity • Treatment-related changes in neutrophils, platelets, lipids, and LFTs • Hepatitis B reactivation	• Hypersensitivity • Monitor for infusion reaction Neutrophils, platelets • LFTs	Elevated IL-6 may downregulate CYP enzymes; use of tocilizumab may lead to increased metabolism of drugs that are CYP450 substrates. Effects on CYP450 may persist for weeks after therapy.	There are insufficient data for the Panel to recommend for or against the use of tocilizumab (AIII). SQ formulation is not intended for IV administration. A list of clinical trials is available here: Tocilizumab
Janus Kinase Inhibitor					
Baricitinib[11]	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; CrCl = creatinine clearance; CRP = C-reactive protein; CYP = cytochrome P; FDA = Food and Drug Administration; IND = Investigational New Drug Application; IV = intravenous; IVIG = intravenous immunoglobulin; LFT = liver function test; MERS = Middle East respiratory syndrome coronavirus; OAT = organic anion transporter; the Panel = COVID-19 Treatment Guidelines Panel; PO = orally; q48h = every 48 hours; RBV = ribavirin; SARS = severe acute respiratory syndrome; SQ = subcutaneous; TACO = transfusion-related circulatory overload; TNF = tumor necrosis factor; TRALI = transfusion-related acute lung injury; ULN = upper limit of normal

Considerations for Certain Concomitant Medications in Patients with COVID-19

Summary Recommendations

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]

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

Name	Affiliation
Co-Chairs	
Roy M. Gulick, MD	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	UNC School of Medicine, Chapel Hill, NC
Jason Baker, MD	Hennepin Healthcare/University of Minnesota, Minneapolis, MN
Roger Bedimo, MD	University of Texas Southwestern/VA North Texas Health Care System, Dallas, TX
Stephen Cantrill, MD	Denver Health, Denver, CO
Ann C. Collier, MD	University of Washington, 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, Detroit, MI
Amy L. Dzierba, PharmD	New York-Presbyterian Hospital, New York, NY
Laura Evans, MD	University of Washington, Seattle, WA
Rajesh Gandhi, MD	Massachusetts General Hospital/Harvard Medical School, Boston, MA
David Glidden, PhD	University of California San Francisco, San Francisco, CA
Birgit Grund, PhD	University of Minnesota, Minneapolis, MN
Erica J. Hardy, MD	Warren Alpert Medical School, Brown University, Providence, RI
Brenna L. Hughes, MD	Duke University School of Medicine, Chapel Hill, 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, PhD	Massachusetts General Hospital/Harvard Medical School, Boston, MA

Name	Affiliation
Co-Chairs	
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	Emory University School of Medicine, Atlanta, GA
Susanna Naggie, MD	Duke University School of Medicine, Durham, NC
Steven Q. Simpson, MD	University of Kansas Medical Center, Kansas City, KS
Susan Swindells, MD	University of Nebraska Medical Center, Omaha, NE
Pablo Tebas, MD	University of Pennsylvania, Philadelphia, PA
Phyllis Tien, MD	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	Department of Veterans Affairs, Washington, DC
Virginia Sheikh, MD	Food and Drug Administration, Silver Spring, MD
Timothy Uyeki, MD	Centers for Disease Control and Prevention, Atlanta, GA
Robert Walker, MD	Biomedical Advanced Research and Development Authority, Washington, DC
U.S. Government Support Team	
Pamela Belperio, PharmD	Department of Veterans Affairs, Los Angeles, CA
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	National Institutes of Health, Bethesda, MD
Robert W. Eisinger, PhD	National Institutes of Health, Bethesda, MD
Elizabeth S. Higgs, MD	National Institutes of Health, Bethesda, MD
Martha C. Nason, PhD	National Institutes of Health, Bethesda, MD
Nitin Seam, MD	National Institutes of Health, Bethesda, MD
Kanal Singh, MD	National Institutes of Health, Bethesda, MD
Assistant Executive Secretaries	
Page Crew, PharmD	National Institutes of Health, Bethesda, MD
Safia Kuriakose, PharmD	Leidos Biomedical Res, Inc., in support of NIAID, Frederick, MD
Andrea M. Lerner, MD	National Institutes of Health, Bethesda, MD

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

Member	Financial Disclosure	
	Company	Relationship
Judith Aberg	Gilead Sciences	Research Support
	Regeneron	Research Support
Adaora Adimora	Gilead Sciences	Consultant, Research Support
Jason Baker	Gilead Science	Research Support
Roger Bedimo	Gilead Sciences	Honoraria
Pamela Belperio	None	N/A
John T. Brooks	None	N/A
Timothy Burges	None	N/A
Stephen Cantrill	None	N/A
Ann C. Collier	None	N/A
Craig Coopersmith	None	N/A
Page Crew	None	N/A
Eric Daar	Gilead Sciences	Consultant, Research Support
Richard T. Davey, Jr.	None	N/A
Susan L. Davis	None	N/A
Amy L. Dzierba	None	N/A
Laurie K. Doepel	None	N/A
Robert W. Eisinger	None	N/A
Laura Evans	None	N/A
Joseph Francis	None	N/A
Rajesh Gandhi	Gilead Sciences	Advisory Board
David Glidden	Gilead Sciences	Consultant
Birgit Grund	None	N/A
Roy M. Gulick	None	N/A
Erica J. Hardy	None	N/A
Elizabeth S. Higgs	None	N/A
Brenna L. Hughes	None	N/A
Steven Johnson	None	N/A
Arthur Kim	None	N/A

Member	Financial Disclosure	
	Company	Relationship
Marla J. Keller	None	N/A
Safia Kuriakose	None	N/A
H. Clifford Lane	None	N/A
Jeffrey L. Lennox	None	N/A
Andrea M. Lerner	None	N/A
Mitchell M. Levy	None	N/A
Gregory Martin	Regeneron	Consultant
Henry Masur	None	N/A
Susanna Naggie	AbbVie	Research Support
	Gilead Sciences	Research Support
	Vir Biotechnology	Advisory Board, Stock Options
Martha C. Naso	None	N/A
Alice K. Pau	None	N/A
Nitin Seam	None	N/A
Virginia Sheikh	None	N/A
Steven Q. Simpson	None	N/A
Kanal Singh	None	N/A
Susan Swindells	None	N/A
Pablo Tebas	Gilead Sciences	Research Support
	Inovio Pharmaceuticals	Research Support
Phyllis Tien	None	N/A
Timothy Uyeki	None	N/A
Alpana A. Waghmare	Ansun BioPharma	Research Support
	KYORIN Pharmaceutical Co.	Advisory Board
Robert Walker	None	N/A
Kevin C. Wilson	None	N/A