COVID-19 Treatment Guidelines*

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

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

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

Introduction

Last Updated: July 8, 2021

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

Panel Composition

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

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

*Наведено окремі розділи Корінніцтва. Матеріал відібрано для застосування в практичній педіатрії. У наступному номері журналу читайте продовження. Повний текст за посиланням: https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf
The inclusion of representatives from professional societies does not imply that their societies have endorsed all elements of these Guidelines.

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

Development of the Guidelines

Each section of the Guidelines is developed by a working group of Panel members with expertise in the area addressed in the section. Each working group is responsible for identifying relevant information and published scientific literature and for conducting a systematic, comprehensive review of that information and literature. The working groups propose updates to the Guidelines based on the latest published research findings and evolving clinical information.

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

Method of Synthesizing Data and Formulating Recommendations

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

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

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

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

- The Panel recommends using [blank] for the treatment of COVID-19 (rating). Recommendations in this category are based on evidence from clinical trials or large cohort studies that demonstrate the clinical or virologic efficacy of a therapy in patients with COVID-19, with the potential benefits outweighing the potential risks.

- There is insufficient evidence for the Panel to recommend either for or against the use of [blank] for the treatment of COVID-19 (no rating). This statement is used when the collective results from clinical trials and/or observational cohorts do not provide the evidence needed to support a recommendation due to too few or conflicting data.

- The Panel recommends against the use of [blank] for the treatment of COVID-19, except in a clinical trial (rating). This recommendation is used for an intervention that has not clearly demonstrated efficacy in the treatment of COVID-19 and/or has potential safety concerns. More clinical trials are needed to further define the role of the intervention.

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

Currently, remdesivir, an antiviral agent, is the only Food and Drug Administration-approved drug for the treatment of COVID-19. An array of drugs approved for other indications and multiple investigational agents are being studied for the treatment of COVID-19 in clinical trials around the globe. These trials can be accessed at ClinicalTrials.gov. In addition, providers can access and prescribe investigational drugs or agents that are approved or licensed for other indications through various mechanisms, including Emergency Use Authorizations (EUAs), Emergency Investigational New Drug (EIND) applications, compassionate use or expanded access programs with drug manufacturers, and/or off-label use.

Whenever possible, the Panel recommends that promising, unapproved, or unlicensed treatments for COVID-19 be studied in well-designed, controlled clinical trials. This recommendation also applies to drugs that have been approved or licensed for indications other than the treatment of COVID-19. The Panel recognizes the critical importance of clinical research in generating evidence to address unanswered questions regarding the safety and efficacy of potential treatments for COVID-19. However, the Panel also realizes that many patients and providers who cannot access these potential treatments via clinical trials still seek guidance about whether to use them.

A large volume of data and publications from randomized controlled trials, observational cohorts, and case series are emerging at a very rapid pace, some in peer-reviewed journals, others as manuscripts that have not yet been peer reviewed, and, in some cases, press releases. The Panel continuously reviews the available data and assesses their scientific rigor and validity. These sources of data and the clinical experiences of the Panel members are used to determine whether new recommendations or changes to the current recommendations are warranted.

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

Overview of COVID-19

Epidemiology

The COVID-19 pandemic has exploded since cases were first reported in China in December 2019. As of July 1, 2021, more than 182 million cases of COVID-19 — caused by SARS-CoV-2 infection — have been reported globally, including more than 3.9 million deaths [1].

Individuals of all ages are at risk for SARS-CoV-2 infection and severe disease. However, the probability of serious COVID-19 disease is higher in people aged ≥60 years, those living in a nursing home or long-term care facility, and those with chronic medical conditions. In an analysis of more than 1.3 million laboratory-confirmed cases that were reported in the United States between January and May 2020, 14% of patients required hospitalization, 2% were admitted to the intensive care unit, and 5% died [2]. The percentage of patients who died was 12 times higher among those with reported medical conditions (19.5%) than among those without medical conditions (1.6%), and the percentage of those who were hospitalized was six times higher among those with reported medical conditions (45.4%) than among those without medical conditions (7.6%). The mortality rate was highest in those aged >70 years, regardless of the presence of chronic medical conditions. Among those with available data on health conditions, 32% had cardiovascular disease, 30% had diabetes, and 18% had chronic lung disease. Other conditions that may lead to a high risk for severe COVID-19 include cancer, kidney disease, obesity, sickle cell disease, and other immunocompromising conditions. Transplant recipients and pregnant people are also at a higher risk of severe COVID-19 [3–10].

Data from the United States suggest that racial and ethnic minorities experience higher rates of COVID-19 and subsequent hospitalization and death [11–15]. However, surveillance data that include race and ethnicity are not available for most reported cases of COVID-19 in the United States [4,16]. Factors that contribute to the increased burden of COVID-19 in these populations may include over-representation in work environments that confer higher risks of exposure to COVID-19, economic inequality (which limits people’s ability to protect themselves against COVID-19 exposure), neighborhood disadvantage [17], and a lack of access to health care [16]. Structural inequalities in society contribute to health disparities for racial and ethnic minority groups, including higher rates of comorbid conditions (e.g., cardiac disease, diabetes, hypertension, obesity, pulmonary diseases), which further increases the risk of developing severe COVID-19 [15].
SARS-CoV-2 Variants

Like other RNA viruses, SARS-CoV-2 is constantly evolving through random mutations. Any new mutations can potentially increase or decrease infectiousness and virulence. In addition, mutations can increase the virus’ ability to evade adaptive immune responses from past SARS-CoV-2 infection or vaccination. This may lead to an increased risk of reinfection or decreased efficacy of vaccines [18]. There is already evidence that some SARS-CoV-2 variants have reduced susceptibility to plasma from people who were previously infected or immunized, as well as to select monoclonal antibodies that are being considered for prevention and treatment [19].

Since December 2020, several variants have been identified that have now been assigned Greek letter designations by the World Health Organization (WHO). These SARS-CoV-2 variants are designated as variants of concern (VoC) if they are associated with select characteristics, such as increase in transmissibility or virulence, decrease in effectiveness of vaccines and/or therapeutics, or interference with diagnostic test targets. WHO has designated variants that are important but not yet fully characterized to meet the criteria for VoC as variants of interest (VoI); however, designations for these variants by other organizations may differ [20]. There is emerging evidence that the B.1.1.7 (Alpha) variant first seen in the United Kingdom is more infectious than earlier variants and may be more virulent [21–23]. It has become the predominant variant in the United Kingdom, and it continues to spread across the globe, including throughout many regions of the United States. The B.1.351 (Beta) variant that was originally identified in South Africa is now the predominant variant in that region and has spread to many other countries, including the United States. The P.1 (Gamma) variant was originally identified in Manaus, Brazil, and has now emerged in the United States. The B.1.617.2 (Delta) variant, first identified in India and designated a VoC by WHO, is also circulating in the United States. Other variants that have emerged in the United States are receiving attention, such as the B.1.427/B.1.429 (Epsilon) variants that were originally identified in California and select VoIs such as the B.1.526 (Iota) variant originally identified in New York and the B.1.617.1 (Kappa) variant first identified in India. For a detailed discussion on the susceptibility of select VoCs and VoIs to available anti-SARS-CoV-2 monoclonal antibodies, please see Anti-SARS CoV-2 Monoclonal Antibodies.

The data on the emergence, spread, and clinical relevance of these new variants is rapidly evolving; this is especially true for research on how variants might affect transmission rates, disease progression, vaccine development, and the efficacy of current therapeutics. Because the research on variants of concern is moving quickly, websites such as the Centers for Disease Control and Prevention’s National Genomic Surveillance Dashboard, CoVariants.org, and WHO’s Tracking SARS-CoV-2 Variants provide regular updates on the data for SARS-CoV-2 variants. The COVID-19 Treatment Guidelines Panel will review the emerging data on these variants, paying particular attention to research on the impacts of these variants on testing, prevention, and treatment.

Clinical Presentation

The estimated incubation period for COVID-19 is up to 14 days from the time of exposure, with a median incubation period of 4 to 5 days [6,24,25]. The spectrum of illness can range from asymptomatic infection to severe pneumonia with acute respiratory distress syndrome and death. Among 72,314 persons with COVID-19 in China, 81% of cases were reported to be mild (defined in this study as no pneumonia or mild pneumonia), 14% were severe (defined as dyspnea, respiratory frequency ≥30 breaths/min, oxygen saturation [SpO₂] ≤93%, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen [PaO₂/FiO₂] <300 mm Hg, and/or lung infiltrates >50% within 24 to 48 hours), and 5% were critical (defined as respiratory failure, septic shock, and/or multiorgan dysfunction or failure) [26]. In a report on more than 370,000 confirmed COVID-19 cases with reported symptoms in the United States, 70% of patients experienced fever, cough, or shortness of breath, 36% had muscle aches, and 34% reported headaches [2]. Other reported symptoms have included, but are not limited to, diarrhea, dizziness, rhinorrhea, anosmia, dysgeusia, sore throat, abdominal pain, anorexia, and vomiting.

The abnormalities seen in chest X-rays of patients with COVID-19 vary, but bilateral multifocal opacities are the most common. The abnormalities seen in computed tomography of the chest also vary, but the most common are bilateral peripheral ground-glass opacities, with areas of consolidation developing later in the clinical course of COVID-19 [27]. Imaging may be normal early in infection and can be abnormal in the absence of symptoms [27].
Common laboratory findings in patients with COVID-19 include leukopenia and lymphopenia. Other laboratory abnormalities have included elevated levels of aminotransferase, C-reactive protein, D-dimer, ferritin, and lactate dehydrogenase.

Although COVID-19 is primarily a pulmonary disease, emerging data suggest that it also leads to cardiac [28,29], dermatologic [30], hematologic [31], hepatic [32], neurologic [33,34], renal [35,36], and other complications.

Thromboembolic events also occur in patients with COVID-19, with the highest risk occurring in critically ill patients [37].

The long-term sequelae of COVID-19 survivors are currently unknown. Persistent symptoms after recovery from acute COVID-19 have been described (see Clinical Spectrum of SARS-CoV-2 Infection). Lastly, SARS-CoV-2 infection has been associated with a potentially severe inflammatory syndrome in children (multisystem inflammatory syndrome in children, or MIS-C) [38,39]. Please see Special Considerations in Children for more information.

References


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

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

**Asymptomatic or Presymptomatic Infection**: Individuals who test positive for SARS-CoV-2 using a virologic test (i.e., a nucleic acid amplification test [NAAT] or an antigen test) but who have no symptoms that are consistent with COVID-19.

**Mild Illness**: Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging.

**Moderate Illness**: Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation (SpO2) >94% on room air at sea level.

**Severe Illness**: Individuals who have SpO2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mm Hg, respiratory frequency >30 breaths/min, or lung infiltrates >50%.

**Critical Illness**: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction. Patients with certain underlying comorbidities are at a higher risk of progressing to severe COVID-19. These comorbidities include being aged 65 years or older; having cardiovascular disease, chronic lung disease, sickle cell disease, diabetes, cancer, obesity, or chronic kidney disease; being pregnant; being a cigarette smoker; and being a recipient of transplant or immunosuppressive therapy. Health care providers should monitor such patients closely until clinical recovery is achieved.

The optimal pulmonary imaging technique has not yet been defined for people with symptomatic SARS-CoV-2 infection. Initial evaluation for these patients may include chest X-ray, ultrasound, or, if indicated, computed tomography. An electrocardiogram should be performed if indicated. Laboratory testing includes a complete blood count with differential and a metabolic profile, including liver and renal function tests. Although inflammatory markers such as C-reactive protein (CRP), D-dimer, and ferritin are not routinely measured as part of standard care, results from such measurements may have prognostic value [2–4].

The definitions for the severity of illness categories listed above also apply to pregnant patients. However, the threshold for certain interventions may be different for pregnant patients and nonpregnant patients. For example, oxygen supplementation is recommended for pregnant patients when SpO2 falls below 95% on room air at sea level to accommodate physiologic changes in oxygen demand during pregnancy and to ensure adequate oxygen delivery to the fetus [5]. If laboratory parameters are used for monitoring pregnant patients and making decisions about interventions, clinicians should be aware that normal physiologic changes during pregnancy can alter several laboratory values. In general, leukocyte cell count increases throughout gestation and delivery and peaks during the immediate postpartum period. This increase is mainly due to neutrophilia [6]. D-dimer and CRP levels also increase during pregnancy and are often higher in pregnant patients than nonpregnant patients [7]. Detailed information on treating COVID-19 in pregnant patients can be found in Special Considerations in Pregnancy and in the pregnancy considerations subsection of each individual section of the Guidelines.

In pediatric patients, radiographic abnormalities are common and, for the most part, should not be the only criteria used to determine the severity of illness. The normal values for respiratory rate also vary with age in children; thus, hypoxia should be the primary criterion used to define severe COVID-19, especially in younger children. In a small number of children and in some young adults, SARS-CoV-2 infection may be followed by a severe inflammatory condition called multisystem inflammatory syndrome in children (MIS-C) [8,9]. This syndrome is discussed in detail in Special Considerations in Children.
Asymptomatic or Presymptomatic Infection

Asymptomatic SARS-CoV-2 infection can occur; although the percentage of patients who remain truly asymptomatic throughout the course of infection is variable and incompletely defined. It is unclear what percentage of individuals who present with asymptomatic infection progress to clinical disease. Some asymptomatic individuals have been reported to have objective radiographic findings that are consistent with COVID-19 pneumonia [10,11]. The availability of widespread virologic testing for SARS-CoV-2 and the development of reliable serologic assays for antibodies to the virus will help determine the true prevalence of asymptomatic and presymptomatic infection. See Therapeutic Management of Nonhospitalized Adults With COVID-19 for recommendations regarding SARS-CoV-2-specific therapy.

Mild Illness

Patients with mild illness may exhibit a variety of signs and symptoms (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell). They do not have shortness of breath, dyspnea on exertion, or abnormal imaging. Most mildly ill patients can be managed in an ambulatory setting or at home through telemedicine or telephone visits. No imaging or specific laboratory evaluations are routinely indicated in otherwise healthy patients with mild COVID-19. Older patients and those with underlying comorbidities are at higher risk of disease progression; therefore, health care providers should monitor these patients closely until clinical recovery is achieved. See Therapeutic Management of Nonhospitalized Adults With COVID-19 for recommendations regarding SARS-CoV-2-specific therapy.

Moderate Illness

Moderate illness is defined as evidence of lower respiratory disease during clinical assessment or imaging, with \(\text{SpO}_2 \geq 94\%\) on room air at sea level. Given that pulmonary disease can progress rapidly in patients with COVID-19, patients with moderate disease should be closely monitored. If bacterial pneumonia or sepsis is suspected, administer empiric antibiotic treatment, re-evaluate the patient daily, and de-escalate or stop antibiotics if there is no evidence of bacterial infection. See Therapeutic Management of Nonhospitalized Adults With COVID-19 for recommendations regarding SARS-CoV-2-specific therapy.

Severe Illness

Patients with COVID-19 are considered to have severe illness if they have \(\text{SpO}_2 < 94\%\) on room air at sea level, a respiratory rate >30 breaths/min, \(\text{PaO}_2/\text{FiO}_2 < 300\ \text{mm Hg}\), or lung infiltrates >50%. These patients may experience rapid clinical deterioration. Oxygen therapy should be administered immediately using a nasal cannula or a high-flow oxygen device. See Therapeutic Management of Hospitalized Adults With COVID-19 for recommendations regarding SARS-CoV-2-specific therapy. If secondary bacterial pneumonia or sepsis is suspected, administer empiric antibiotics, re-evaluate the patient daily, and de-escalate or stop antibiotics if there is no evidence of bacterial infection.

Critical Illness

Critically ill patients may have acute respiratory distress syndrome, septic shock that may represent virus-induced distributive shock, cardiac dysfunction, an exaggerated inflammatory response, and/or exacerbation of underlying comorbidities. In addition to pulmonary disease, patients with critical illness may also experience cardiac, hepatic, renal, central nervous system, or thrombotic disease. As with any patient in the intensive care unit (ICU), successful clinical management of a patient with COVID-19 includes treating both the medical condition that initially resulted in ICU admission and other comorbidities and nosocomial complications.

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

SARS-CoV-2 Reinfection

As seen with other viral infections, reinfection with SARS-CoV-2 after recovery from prior infection has been reported [12]. The true prevalence of reinfection is not known, although there are concerns that it may occur with increased frequency with the circulation of new variants [13]. SARS-CoV-2 can often be detected from nasal swab for weeks to months after initial infection, therefore, repeat testing to evaluate for reinfection should be considered only for those who have recovered from initial infection and present with COVID-19-compatible symptoms with no obvious alternate etiology (AIII) [14].
Diagnostic testing in this setting is summarized in Testing for SARS-CoV-2 Infection. In addition, if reinfection is suspected, guidelines for the diagnosis and evaluation of suspected SARS-CoV-2 reinfection are provided by the Centers for Disease Control and Prevention (CDC) [15].

It has been speculated that reinfection may occur more frequently in those with a less robust immune response during the initial infection, as is often reported in those with mild illness. Reinfection may also occur as initial immune responses wane over time. Nevertheless, one review noted that SARS-CoV-2 reinfection occurred after previous severe disease in three cases and as early as 3 weeks after diagnosis of the initial infection [16]. A public site posts a variety of published and unpublished reports of reinfection, noting that it has been described to occur from as early as a few weeks to many months after initial infection, and occasionally follows episodes of severe COVID-19 [17]. Although data are limited, there is no evidence to suggest that the treatment of highly suspected or documented SARS-CoV-2 reinfection should be different from that for initial infection as outlined in Therapeutic Management of Nonhospitalized Adults With COVID-19 and Therapeutic Management of Hospitalized Adults With COVID-19.

**Persistent Symptoms or Organ Dysfunction After Acute COVID-19**

There have been an increasing number of reports of patients who experience persistent symptoms and/or organ dysfunction after acute COVID-19. Data about the incidence, natural history, and etiology of these symptoms are emerging. However, these reports have several limitations, including lack of an agreed-upon case definition and potential bias as most reports included only patients who attended post-COVID-19 clinics and no comparator groups. No specific treatments for the persistent effects of COVID-19 have yet been identified, although this COVID-19 rapid guideline proposes general management strategies.

The nomenclature for this phenomenon is evolving, and there is no established clinical terminology to date. It has been referred to as post-COVID-19 condition or colloquially, «long COVID», and affected patients have been referred to as «long haulers.» The term «post-acute sequelae of COVID-19» (PASC) has also been used to describe late sequelae of SARS-CoV-2 infection that include these persistent symptoms, as well as other delayed syndromes such as MIS-C and multisystem inflammatory syndrome in adults (MIS-A). To date, no case definition and no specific time frame have been established to define the syndrome of persistent symptoms and/or organ dysfunction after acute COVID-19. However, CDC recently proposed defining late sequelae as sequelae that extend >4 weeks after initial infection [18,19]. The Patient-Led Research Collaborative for COVID-19 defines long COVID as a collection of symptoms that develop during or following a confirmed or suspected case of COVID-19 and that continue for >28 days [20]. Incidence rates vary widely, from about 10% in some reports to one cohort study in which 87% of patients reported at least one persistent symptom [21].

Some of the symptoms overlap with the post-intensive care syndrome (PICS) that has been described in patients without COVID-19, but prolonged symptoms and disabilities after COVID-19 have also been reported in patients with milder illness, including outpatients (see General Considerations for information on PICS) [22,23].

Despite limitations of the available descriptive data related to these persistent symptoms, some representative studies have suggested that common findings include fatigue, joint pain, chest pain, palpitations, shortness of breath, cognitive impairment, and worsened quality of life [24,25].

CDC conducted a telephone survey of a random sample of 292 adult outpatients who had positive polymerase chain reaction results for SARS-CoV-2. Among the 274 respondents who were symptomatic at the time of testing, 35% reported not having returned to their usual state of health 2 weeks or more after testing; 26% among patients aged 18 to 34 years, 32% among those aged 35 to 49 years, and 47% among those aged ≥50 years [23]. An age of ≥50 years and the presence of three or more chronic medical conditions were associated with not returning to usual health within 14 to 21 days. Moreover, one in five individuals aged 18 to 34 years who did not have chronic medical conditions had not returned to baseline health when interviewed at a median of 16 days from the testing date.

In a cohort study from Wuhan, China, 1,733 discharged patients with COVID-19 were evaluated for persistent symptoms at a median of 186 days after symptom onset [26]. The most common symptoms were fatigue or muscle weakness and sleep difficulties (reported among 63% and 26% of participants, respectively). Anxiety or depression was reported among 23% of patients.

In a longitudinal prospective cohort of mostly outpatients with laboratory-confirmed SARS-CoV-2 infection at the University of Washington, 177 participants completed a follow-up questionnaire.
between 3 and 9 months after illness onset [27]. Overall, 91% of the respondents were outpatients (150 with mild illness and 11 with no symptoms), and only 9.0% had moderate or severe disease requiring hospitalization. Among those reporting symptoms, 33% of the outpatients and 31% of the hospitalized patients reported at least one persistent symptom. Persistent symptoms were reported by 27% of the patients aged 18 to 39 years, 30% aged 40 to 64 years, and 43% aged ≥65 years. The most common persistent symptoms were loss of sense of smell or taste and fatigue (both reported by 14% of participants).

**Fatigue**

The prevalence of fatigue among 128 individuals from Ireland who had recovered from the acute phase of COVID-19 was examined using the Chalder Fatigue Scale (CFQ11). More than half of patients (67 of 128 patients [52.3%]) reported persistent fatigue at a median of 10 weeks after initial symptoms first appeared. There was no association between illness severity and fatigue [28]. An outpatient service for patients recovering from acute COVID-19 developed in Italy reported that 87% of 143 patients surveyed reported persistent symptoms at a mean of 60 days after symptom onset, with the most common symptom being fatigue (which occurred in 53.1% of these patients) [21].

**Cardiopulmonary**

A study from the United Kingdom reported that among 100 hospitalized patients (32 received care in the ICU and 68 received care in hospital wards only), 72% of the ICU patients and 60% of the ward patients experienced fatigue and breathlessness at 4 to 8 weeks after hospital discharge. The authors suggested that posthospital rehabilitation may be necessary for some of these patients [24]. A retrospective study from China found that pulmonary function (as measured by spirometry) was still impaired 1 month after hospital discharge in 31 of 57 patients (54.4%) [29]. In a study from Germany that included 100 patients who had recently recovered from COVID-19, cardiac magnetic resonance imaging (MRI) performed a median of 71 days after diagnosis revealed cardiac involvement in 78% of patients and ongoing myocardial inflammation in 60% of patients [30]. A retrospective study from China of 26 patients who had recovered from COVID-19 and who had initially presented with cardiac symptoms found abnormalities on cardiac MRI in 15 patients (58%) [31]. The assessment of the prevalence of cardiac abnormalities in people with post-acute COVID-19 syndrome should be viewed with caution, however, as the analysis included only patients with cardiac symptoms.

**Neuropsychiatric**

Neurologic and psychiatric symptoms have also been reported among patients who have recovered from acute COVID-19. High rates of anxiety and depression have been reported in some patients using self-report scales for psychiatric distress [25,32]. Younger patients have been reported to experience more psychiatric symptoms than patients aged ≥60 years [24,25]. Patients may continue to experience headaches, vision changes, hearing loss, loss of taste or smell, impaired mobility, numbness in extremities, tremors, myalgia, memory loss, cognitive impairment, and mood changes for up to 3 months after diagnosis of COVID-19 [33–35]. One study in the United Kingdom administered cognitive tests to 84,285 participants who had recovered from suspected or confirmed SARS-CoV-2 infection. These participants had worse performances across multiple domains than would be expected for people with the same ages and demographic profiles; this effect was observed even among those who had not been hospitalized [36]. However, the study authors did not report when the tests were administered in relation to the diagnosis of COVID-19.

Persistent symptoms after acute COVID-19 have also been reported in pregnant people [37]. Systematic data on persistent symptoms in children following recovery from the acute phase of COVID-19 are not currently available, although case reports suggest that children may experience long-term effects similar to those experienced by adults after clinical COVID-19 [38,39]. MIS-C is discussed in Special Considerations in Children.

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


Two main processes are thought to drive the pathogenesis of COVID-19. Early in the clinical course, the disease is primarily driven by the replication of SARS-CoV-2. Later in the clinical course, the disease appears to be driven by a dysregulated immune/inflammatory response to SARS-CoV-2 that leads to tissue damage. Based on this understanding, it is anticipated that therapies that directly target SARS-CoV-2 would have the greatest effect early in the course of the disease, while immunosuppressive/anti-inflammatory therapies are likely to be more beneficial in the later stages of COVID-19.

The clinical spectrum of SARS-CoV-2 infection includes asymptomatic or presymptomatic infection and mild, moderate, severe, and critical illness. Figure 1 provides guidance for clinicians on the therapeutic management of nonhospitalized adult patients. This includes patients who do not require hospitalization or supplemental oxygen and those who have been discharged from an emergency department or a hospital. Figure 2 provides guidance on the therapeutic management of hospitalized adult patients according to their disease severity and oxygen requirements.
### General Management of Nonhospitalized Patients With Acute COVID-19

_Last Updated: July 8, 2021_

**Summary Recommendations**

Management of nonhospitalized patients with acute COVID-19 should include providing supportive care, taking steps to reduce the risk of SARS-CoV-2 transmission (including isolating the patient), and advising patients on when to contact a health care provider and seek an in-person evaluation (AIII).

When possible, patients with symptoms of COVID-19 should be triaged via telehealth visits before receiving in-person care. Patients with dyspnea should be referred for an in-person evaluation by a health care provider and should be followed closely during the initial days after the onset of dyspnea to assess for worsening respiratory status (AIII).

Management plans should be based on a patient's vital signs, physical exam findings, risk factors for progression to severe illness, and the availability of health care resources (AIII).

See Therapeutic Management of Nonhospitalized Adults With COVID-19 for specific recommendations on using pharmacologic therapy in nonhospitalized patients.

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

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

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### Therapeutic Management of Hospitalized Adults With COVID-19 Based on Disease Severity

**Panel’s Recommendations**

- **Hospitalized but Does Not Require Supplemental Oxygen**
  - Use one of the following options:
    - Remdesivir (e.g., for patients who require minimal supplemental oxygen) (BIIa)
    - Dexamethasone plus remdesivir (e.g., for patients who require increasing amounts of supplemental oxygen) (BIIa)
    - Dexamethasone (when combination with remdesivir cannot be used or is not available) (BII)

- **Hospitalized and Requires Supplemental Oxygen**
  - For recently hospitalized patients with rapidly increasing oxygen needs and systemic inflammation:
    - Add either baricitinib (BIIa) or IV tocilizumab (BIIa) to one of the two options above
    - If neither baricitinib nor IV tocilizumab is available or feasible to use, tocilizumab can be used instead of baricitinib (BIIa) or IV sarilumab can be used instead of IV tocilizumab (BIIa)

- **Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation**
  - Dexamethasone (A)

- **Hospitalized and Requires IMV or ECMO**
  - Dexamethasone (A)

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

- If patients progress to requiring high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO, complete remdesivir course.
- For example, within 3 days of hospital admission.
- Drugs are listed alphabetically and not in order of preference. As there are no studies directly comparing baricitinib and tocilizumab for treatment of COVID-19, there is insufficient evidence to recommend one drug over the other. Treatment decisions should be determined by local guidance, drug availability, and patient comorbidities.

Key: ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; IMV = invasive mechanical ventilation; IV = intravenous; the Panel = the COVID-19 Treatment Guidelines Panel; PO = orally
Introduction

This section of the Guidelines is intended to provide information to health care providers who are caring for nonhospitalized patients with COVID-19. The COVID-19 Treatment Guidelines Panel's (the Panel) recommendations for pharmacologic management can be found in Therapeutic Management of Nonhospitalized Adults With COVID-19. The Panel recognizes that the distinction between outpatient and inpatient care may be less clear during the COVID-19 pandemic. Patients with COVID-19 may receive care outside traditional ambulatory care or hospital settings if there is a shortage of hospital beds, staff, or resources. Settings such as field hospitals and ambulatory surgical centers and programs such as Acute Hospital Care at Home have been implemented to alleviate hospital bed and staffing shortages [1]. Patients may enter an Acute Hospital Care at Home program from either an emergency department (ED) or an inpatient hospital setting. Health care providers should use their judgment when deciding whether the guidance offered in this section applies to individual patients.

This section focuses on the evaluation and management of:
- Adults with COVID-19 in an ambulatory care setting;
- Adults with COVID-19 following discharge from the ED; and
- Adults with COVID-19 following inpatient discharge.

Outpatient evaluation and management in each of these settings may include some or all of the following: telemedicine, remote monitoring, in-person visits, and home visits by nurses or other health care providers.

Managing Patients With COVID-19 in an Ambulatory Care Setting

Approximately 80% of patients with COVID-19 have mild illness that does not warrant medical intervention or hospitalization [2]. Most patients with mild COVID-19 (defined as the absence of viral pneumonia and hypoxemia) can be managed in an ambulatory care setting or at home. Patients with moderate COVID-19 (those with viral pneumonia but without hypoxemia) or severe COVID-19 (those with dyspnea, hypoxemia, or lung infiltrates >50%) need in-person evaluation and close monitoring, as pulmonary disease can progress rapidly and require hospitalization [3].

Health care providers should identify patients who may be at high risk for progression to severe COVID-19; these patients may be candidates for anti-SARS-CoV-2 monoclonal antibody treatment (see Figure 1 in Therapeutic Management of Nonhospitalized Adults with COVID-19). Management of COVID-19 patients in the outpatient setting should focus on providing supportive care, taking steps to reduce the risk of SARS-CoV-2 transmission (e.g., wearing a mask, isolating the patient) [4,5], and advising patients on when to seek in-person evaluation [6]. Supportive care includes managing symptoms (as described below), ensuring that patients are receiving the proper nutrition, and paying attention to the risks of social isolation, particularly in older adults [7]. Other unique aspects of care for geriatric patients with COVID-19 include considerations related to cognitive impairment, frailty, fall risk, and polypharmacy. Older patients and those with chronic medical conditions have a higher risk for hospitalization and death; however, SARS-CoV-2 infection may cause severe disease and death in patients of any age, even in the absence of any risk factors. The decision to monitor a patient in the outpatient setting should be made on a case-by-case basis.

Assessing the Need for In-Person Evaluation

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

All patients with dyspnea, oxygen saturation (SpO2) ≤94% on room air at sea level (if this information is available), or symptoms that suggest higher acuity (e.g., chest pain or tightness, dizziness, confusion or other mental status changes) should be referred for an in-person evaluation by a health care provider. The criteria used to determine the appropriate clinical setting for an in-person evaluation may vary by location and institution; it may also change over time as new data and treatment options emerge. There should be a low threshold for in-person evaluation of older persons and those with medical con-
Clinical Considerations When Managing Patients in an Ambulatory Care Setting

Persons who have symptoms that are compatible with COVID-19 should undergo diagnostic SARS-CoV-2 testing (see Prevention and Prophylaxis of SARS-CoV-2 Infection). Patients with SARS-CoV-2 infection may be asymptomatic or experience symptoms that are indistinguishable from other acute viral or bacterial infections (e.g., fever, cough, sore throat, malaise, muscle pain, headache, gastrointestinal symptoms). It is important to consider other possible etiologies of symptoms, including other respiratory viral infections (e.g., influenza), community-acquired pneumonia, congestive heart failure, asthma or chronic obstructive pulmonary disease exacerbations, and streptococcal pharyngitis.

In most adult patients, if dyspnea develops, it tends to occur between 4 and 8 days after symptom onset, although it can also occur after 10 days [13]. While mild dyspnea is common, worsening dyspnea and severe chest pain/tightness suggest the development or progression of pulmonary involvement. In studies of patients who developed acute respiratory distress syndrome, progression occurred a median of 2.5 days after the onset of dyspnea [14–16]. Adult outpatients with dyspnea should be followed closely with telehealth or in-person monitoring, particularly during the first few days following the onset of dyspnea, to monitor for worsening respiratory status (AIII).

If an adult patient has access to a pulse oximeter at home, \(\text{SpO}_2\) measurements can be used to help assess overall clinical status. Patients should be advised to use pulse oximeters on warm fingers rather than cold fingers for better accuracy. Patients should inform their health care provider if the value is repeatedly below 95% on room air at sea level. Pulse oximetry may not accurately detect occult hypoxemia, especially in Black patients [3,17,18]. Additionally, \(\text{SpO}_2\) readings obtained through a mobile phone application may not be accurate enough for clinical use [19–21]. Importantly, oximetry should only be interpreted within the context of a patient’s entire clinical presentation (i.e., results should be disregarded if a patient is complaining of increasing dyspnea).

Counseling Regarding the Need for Follow-Up

Health care providers should identify patients who are at high risk for disease progression. These patients may be candidates for anti-SARS-CoV-2 monoclonal antibody treatments, and clinicians should ensure that these patients receive adequate medical follow-up. The frequency and duration of follow-up will depend on the risk for severe disease, the severity of symptoms, and the patient’s ability to self-report worsening symptoms. Health care providers should determine whether a patient has access to a phone, computer, or tablet for telehealth; whether they have adequate transportation for clinic visits; and whether they have regular access to food. The clinician should also confirm that the patient has a caregiver who can assist with daily activities if needed.

All patients and/or their family members or caregivers should be counseled about the warning symptoms that should prompt re-evaluation through a telehealth visit or an in-person evaluation in an ambulatory care setting or ED. These symptoms include new onset of dyspnea; worsening dyspnea (particularly if dyspnea occurs while resting or if it interferes with daily activities); dizziness; and mental status changes, such as confusion. Patients should be educated about the time course of these symptoms and the possible respiratory decline that may occur, on average, 1 week after the onset of illness.

Managing Adults With COVID-19 Following Discharge from the Emergency Department

There are no fixed criteria for admitting patients with COVID-19 to the hospital; criteria may vary by region and hospital facilities. Patients with severe disease are typically admitted to the hospital, but...
some patients with severe disease may not be admitted due to a high prevalence of infection and limited hospital resources. In addition, patients who could receive appropriate care at home but are unable to be adequately managed in their usual residential setting are candidates for temporary shelter in supervised facilities, such as a COVID-19 alternative care facility [22]. For example, patients who are living in multigenerational households or who are homeless may not be able to self-isolate and should be provided resources such as dedicated housing units or hotel rooms, when available. Unfortunately, dedicated residential care facilities for COVID-19 patients are not widely available, and community-based solutions for self-care and isolation should be explored.

Treatment with an anti-SARS-CoV-2 monoclonal antibody is recommended for patients with mild to moderate COVID-19 who are not on supplemental oxygen and who have been discharged from the ED but who are at high risk for clinical progression (see Therapeutic Management of Nonhospitalized Adults With COVID-19).

In the cases where institutional resources (e.g., inpatient beds, staff members) are scarce, it may be necessary to discharge an adult patient and provide an advanced level of home care, including supplemental oxygen (if indicated), pulse oximetry, and close follow-up. Although early discharge of those with severe disease is not generally recommended by the Panel, it is recognized that these management strategies are sometimes necessary. In these situations, some institutions are providing frequent telemedicine follow-up visits for these patients or providing a hotline for patients to speak with a clinician when necessary. Home resources should be assessed before a patient is discharged from the ED; outpatients should have a caregiver and access to a device that is suitable for telehealth. Patients and/or their family members or caregivers should be counseled about the warning symptoms that should prompt re-evaluation by a health care provider. Special consideration may be given to using certain therapeutics (e.g., dexamethasone) in this setting. For more information, see Therapeutic Management of Nonhospitalized Adults With COVID-19.

Anticoagulants and antiplatelet therapy should not be initiated in the ED for the prevention of venous thromboembolism (VTE) or arterial thrombosis if the patient is not being admitted to the hospital, unless the patient has other indications for the therapy or is participating in a clinical trial (AIII). For more information, see Antithrombotic Therapy in Patients With COVID-19. Patients should be encouraged to ambulate, and activity should be increased according to the patient’s tolerance.

Managing Adults With COVID-19 Following Hospital Discharge

Most patients who are discharged from the hospital setting should have a follow-up visit with a health care provider soon after discharge. Whether an in-person or telehealth visit is most appropriate depends on the clinical and social situation. In some cases, adult patients are deemed to be stable for discharge from the inpatient setting even though they still require supplemental oxygen. Special consideration may be given to using certain therapeutics (e.g., dexamethasone) in this setting. For more information, see Therapeutic Management of Nonhospitalized Adults With COVID-19. When possible, these individuals should receive oximetry monitoring and close follow-up through telehealth visits, visiting nurse services, or in-person clinic visits.

Hospitalized patients with COVID-19 should not be routinely discharged while receiving VTE prophylaxis, unless they have another indication or are participating in a clinical trial (AIII). For more information, see Antithrombotic Therapy in Patients With COVID-19. Patients should be encouraged to ambulate, and activity should be increased according to the patient’s tolerance.

Considerations in Pregnancy

Managing pregnant outpatients with COVID-19 is similar to managing nonpregnant patients (see Special Considerations in Pregnancy). Clinicians should offer supportive care, take steps to reduce the risk of SARS-CoV-2 transmission, and provide guidance on when to seek an in-person evaluation. The American College of Obstetricians and Gynecologists (ACOG) has developed an algorithm to aid the practitioner in evaluating and managing pregnant outpatients with laboratory-confirmed or suspected COVID-19 [23]. ACOG has also published recommendations on how to use telehealth for prenatal care and how to modify routine prenatal care when necessary to decrease the risk of SARS-CoV-2 transmission to patients, caregivers, and staff.

In pregnant patients, SpO2 should be maintained at 95% or above on room air at sea level; therefore, the threshold for monitoring pregnant patients in an inpatient setting may be lower than in nonpregnant patients [24]. In general, there are no changes to fetal monitoring recommendations in the outpa-
tient setting, and fetal management should be similar to the fetal management used for other pregnant patients with medical illness [25]. However, these monitoring strategies can be discussed on a case-by-case basis with an obstetrician. Pregnant and lactating patients should be given the opportunity to participate in clinical trials of outpatients with COVID-19 to help inform decision-making in this population.

**Considerations in Children**

Children and adolescents with acute COVID-19 are less likely than adults to require medical intervention or hospitalization, and most can be managed in an ambulatory care setting or at home. In general, the need for ED evaluation or hospitalization should be based on the patient’s vital signs, physical exam findings (e.g., dyspnea), and risk factors for progression to severe illness. Certain groups, including young infants, children with risk factors, and those with presentations that overlap with multisystem inflammatory syndrome in children (MIS-C), may require hospitalization for more intensive monitoring. However, this should be determined on a case-by-case basis.

Most children with mild or moderate COVID-19, even those with risk factors, will not progress to more severe illness and will recover without specific therapy (see Special Considerations in Children). There is insufficient evidence for the Panel to recommend either for or against the use of anti-SARS-CoV-2 monoclonal antibody products in nonhospitalized children with COVID-19 who have risk factors for severe disease. The available efficacy data for adults suggests that anti-SARS-CoV-2 monoclonal antibody products may be considered for use in children who meet the Food and Drug Administration Emergency Use Authorization (EUA) criteria, especially those who have more than one risk factor. The decision to use these products in children should be made on a case-by-case basis in consultation with a pediatric infectious disease specialist. The risk factors that predict progression to severe disease in adults can be used to determine the risk of progression in children aged ≥16 years (see the Panel’s statement on the EUAs for anti-SARS-CoV-2 monoclonal antibodies).

In general, pediatric patients should not continue receiving remdesivir, dexamethasone, or other COVID-19-directed therapies following discharge from an ED or an inpatient setting. Clinicians should refer to Special Considerations in Children for more information on the management of children with COVID-19.

**References**


Care of Critically Ill Adult Patients With COVID-19

Summary Recommendations

Infection Control
- For health care workers who are performing aerosol-generating procedures on patients with COVID-19, the COVID-19 Treatment Guidelines Panel (the Panel) recommends using an N95 respirator (or equivalent or higher-level respirator) rather than surgical masks, in addition to other personal protective equipment (PPE) (i.e., gloves, gown, and eye protection such as a face shield or safety goggles) (AI).
- The Panel recommends minimizing the use of aerosol-generating procedures on intensive care unit patients with COVID-19 and carrying out any necessary aerosol-generating procedures in a negative-pressure room, also known as an airborne infection isolation room, when available (AII).
- For health care workers who are providing usual care for nonventilated patients with COVID-19, the Panel recommends using an N95 respirator (or equivalent or higher-level respirator) or a surgical mask in addition to other PPE (i.e., gloves, gown, and eye protection such as a face shield or safety goggles) (AI).
- For health care workers who are performing non-aerosol-generating procedures on patients with COVID-19 who are on closed-circuit mechanical ventilation, the Panel recommends using an N95 respirator (or equivalent or higher-level respirator) in addition to other PPE (i.e., gloves, gown, and eye protection such as a face shield or safety goggles) because ventilator circuits may become disrupted unexpectedly (BII).

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

Hemodynamics
- For adults with COVID-19 and shock, the Panel recommends using dynamic parameters, skin temperature, capillary refill time, and/or lactate levels over static parameters to assess fluid responsiveness (BII).
- For the acute resuscitation of adults with COVID-19 and shock, the Panel recommends using buffered/balanced crystalloids over unbalanced crystalloids (BII).
- For the acute resuscitation of adults with COVID-19 and shock, the Panel recommends against the initial use of albumin for resuscitation (BII).
- For adults with COVID-19 and shock, the Panel recommends norepinephrine as the first-choice vasopressor (AII).
- For adults with COVID-19 and shock, the Panel recommends titrating vasoactive agents to target a mean arterial pressure (MAP) of 60 to 65 mm Hg over higher MAP targets (BII).

<...>
The Panel recommends against using hydroxyethyl starches for intravascular volume replacement in patients with sepsis or septic shock (AI).

When norepinephrine is available, the Panel recommends against using dopamine for patients with COVID-19 and shock (AI).

As a second line vasopressor, the Panel recommends adding either vasopressin (up to 0.03 units/min) (BIIa) or epinephrine (BIIb) to norepinephrine to raise MAP to target or adding vasopressin (up to 0.03 units/min) (BIIa) to decrease norepinephrine dosage.

The Panel recommends against using low-dose dopamine for renal protection (AI).

The Panel recommends using dobutamine in patients who show evidence of cardiac dysfunction and persistently 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 (BII).

For adults with refractory septic shock who have completed a course of corticosteroids to treat their COVID-19, the Panel recommends using low-dose corticosteroid therapy (“shock-reversal”) over no corticosteroid therapy (BII).

Oxygenation and Ventilation

For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy, the Panel recommends high-flow nasal cannula (HFNC) oxygen over noninvasive positive pressure ventilation (NIPPV) (BIIa).

In the absence of an indication for endotracheal intubation, the Panel recommends a closely monitored trial of NIPPV for adults with COVID-19 and acute hypoxemic respiratory failure and for whom HFNC is not available (BIIa).

For patients with persistent hypoxemia despite increasing supplemental oxygen requirements in whom endotracheal intubation is not otherwise indicated, the Panel recommends considering a trial of awake prone positioning to improve oxygenation (CIIa).

The Panel recommends using awake prone positioning as a rescue therapy for refractory hypoxemia to avoid intubation in patients who otherwise meet the indications for intubation and mechanical ventilation (AIII).

If intubation becomes necessary, the procedure should be performed by an experienced practitioner in a controlled setting due to the enhanced risk of exposing health care practitioners to SARS-CoV-2 during intubation (AIII).

For mechanically ventilated adults with COVID-19 and acute respiratory distress syndrome (ARDS):

- The Panel recommends using low tidal volume (VT) ventilation (VT 4–8 mL/kg of predicted body weight) over higher VT ventilation (VT >8 mL/kg) (AI).

- The Panel recommends targeting plateau pressures of <30 cm H2O (AIa).

- The Panel recommends using a conservative fluid strategy over a liberal fluid strategy (BIIa).

- The Panel recommends using the routine use of inhaled nitric oxide (Alla).

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

  - The Panel recommends using a higher positive end-expiratory pressure (PEEP) strategy over a lower PEEP strategy (BIIa).

  - For mechanically ventilated adults with COVID-19 and refractory hypoxemia despite optimized ventilation, the Panel recommends prone ventilation for 12 to 16 hours per day over no prone ventilation (BIIa).

  - The Panel recommends using, as needed, intermittent boluses of neuromuscular blocking agents (NMBA) or continuous NMBA infusion to facilitate protective lung ventilation (BIIa).

  - In the event of persistent patient-ventilator dysynchrony, or in cases where a patient requires ongoing deep sedation, prone ventilation, or persistently high plateau pressures, the Panel recommends using a continuous NMBA infusion for up to 48 hours as long as patient anxiety and pain can be adequately monitored and controlled (BIII).

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

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

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

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

Acute Kidney Injury and Renal Replacement Therapy

- For critically ill patients with COVID-19 who have acute kidney injury and who develop indications for renal replacement therapy, the Panel recommends continuous renal replacement therapy (CRRT), if available (BIII).

- If CRRT is not available or not possible due to limited resources, the Panel recommends prolonged intermittent renal replacement therapy rather than intermittent hemodialysis (BIII).

Pharmacologic Interventions

- In patients with COVID-19 and severe or critical illness, there is insufficient evidence for the Panel to recommend either for or against empiric broad-spectrum antimicrobial therapy in the absence of another indication.

- If antimicrobials are initiated, the Panel recommends that their use should be reassessed daily to minimize the adverse consequences of unnecessary antimicrobial therapy (AIII).

Extracorporeal Membrane Oxygenation

- There is insufficient evidence for the Panel to recommend either for or against the use of extracorporeal membrane oxygenation for patients with COVID-19 and refractory hypoxemia.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials without major limitations; IIA = Other randomized trials or subgroup analyses of randomized trials; IIB = Nonrandomized trials or observational cohort studies; III = Expert opinion
General Considerations
Last Updated: April 21, 2021

Severe cases of COVID-19 may be associated with hypoxemic respiratory failure, acute respiratory distress syndrome (ARDS), septic shock, cardiac dysfunction, elevation in multiple inflammatory cytokines, thromboembolic disease, and/or exacerbation of underlying comorbidities. In addition to pulmonary disease, patients with COVID-19 may also experience cardiac, hepatic, renal, and central nervous system disease. Because patients with critical illness are likely to undergo aerosol-generating procedures, they should be placed in airborne infection isolation rooms, when available.

Guidance on diagnostic testing for SARS-CoV-2 can be found in the Testing for SARS-CoV-2 Infection section.

Most of the recommendations for the management of critically ill patients with COVID-19 are extrapolated from experience with other causes of sepsis [1]. Currently, there is limited information to suggest that the critical care management of patients with COVID-19 should differ substantially from the management of other critically ill patients; however, special precautions to prevent environmental contamination by SARS-CoV-2 are warranted.

As with any patient in the intensive care unit (ICU), successful clinical management of a patient with COVID-19 includes treating both the medical condition that initially resulted in ICU admission and other comorbidities and nosocomial complications.

Comorbid Conditions
Certain attributes and comorbidities (e.g., older age, cardiovascular disease, diabetes, chronic obstructive pulmonary disease, cancer, renal disease, obesity, sickle cell disease, receipt of a solid organ transplant) are associated with an increased risk of severe illness from COVID-19 [2].

Bacterial Superinfection of COVID-19-Associated Pneumonia
Limited information exists about the frequency and microbiology of pulmonary coinfections and superinfections in patients with COVID-19, such as hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP). Some studies from China emphasize the lack of bacterial coinfections in patients with COVID-19, while other studies suggest that these patients experience frequent bacterial complications [3–8]. There is appropriate concern about performing pulmonary diagnostic procedures such as bronchoscopy or other airway sampling procedures that require disruption of a closed airway circuit in patients with COVID-19. Thus, while some clinicians do not routinely start empiric broad-spectrum antimicrobial therapy for patients with severe COVID-19 disease, other experienced clinicians routinely use such therapy. However, empiric broad-spectrum antimicrobial therapy is the standard of care for the treatment of shock. Antibiotic stewardship is critical to avoid reflexive or continued courses of antibiotics.

Inflammatory Response Due to COVID-19
Patients with COVID-19 may express increased levels of pro-inflammatory cytokines and anti-inflammatory cytokines, which has previously been referred to as «cytokine release syndrome» or «cytokine storm», although these are imprecise terms. However, these terms are misnomers because the magnitude of cytokine elevation in patients with COVID-19 is modest compared to that in patients with many other critical illnesses, such as sepsis and ARDS [9,10].

Patients with COVID-19 and severe pulmonary involvement are well described to also manifest extrapulmonary disease and to exhibit laboratory markers of acute inflammation. Patients with these manifestations of severe pulmonary disease typically progress to critical illness 10 to 12 days after the onset of COVID-19 symptoms.

Multisystem Inflammatory Syndrome in Adults
In addition, there are case reports describing patients who had evidence of acute or recent SARS-CoV-2 infection (documented by a nucleic acid amplification test [NAAT] or antigen or antibody testing) with minimal respiratory symptoms, but with laboratory markers of severe inflammation (e.g., elevated C-reactive protein [CRP], ferritin, D-dimer, cardiac enzymes, liver enzymes, and creatinine) and various other symptoms, including fever and shock; and signs of cardiovascular, gastrointestinal, dermatologic, and neurologic disease. This constellation of signs and symptoms has been designated multisystem inflammatory syndrome in adults (MIS-A) [11]. To date, most adults in whom MIS-A has
been described have survived. This syndrome is similar to a syndrome previously described in children (multisystem inflammatory syndrome in children [MIS-C]).

MIS-A is defined by the following criteria:
1. A severe illness requiring hospitalization in an individual aged ≥21 years;
2. Current or past infection with SARS-CoV-2;
3. Severe dysfunction in one or more extrapulmonary organ systems;
4. Laboratory evidence of elevated inflammatory markers (e.g., CRP, ferritin, D-dimer, interleukin [IL]-6);
5. Absence of severe respiratory illness; and
6. Absence of an alternative unifying diagnosis.11

Because there is no specific diagnostic test for MIS-A, diagnosis of this inflammatory syndrome is one of exclusion after other causes (e.g., septic shock) have been eliminated. Although there are currently no controlled clinical trial data in patients with MIS-A to guide treatment of the syndrome, case reports have described the use of intravenous immunoglobulin, corticosteroids, or anti-IL-6 therapy.

COVID-19-Induced Cardiac Dysfunction, Including Myocarditis
A growing body of literature describes cardiac injury or dysfunction in approximately 20% of patients who are hospitalized with COVID-19 [4,6,12–15]. COVID-19 may be associated with an array of cardiovascular complications, including acute coronary syndrome, myocarditis, arrhythmias, and thromboembolic disease [16].

Thromboembolic Events and COVID-19
Critically ill patients with COVID-19 have been observed to have a prothrombotic state, which is characterized by the elevation of certain biomarkers, and there is an apparent increase in the incidence of venous thromboembolic disease in this population. In some studies, thromboemboli have been diagnosed in patients who received chemical prophylaxis with heparinoids [17–19]. Autopsy studies provide additional evidence of both thromboembolic disease and microvascular thrombosis in patients with COVID-19 [20]. Some authors have called for routine surveillance of ICU patients for venous thromboembolism [21]. See the Antithrombotic Therapy in Patients with COVID-19 section for a more detailed discussion.

Renal and Hepatic Dysfunction Due to COVID-19
Although SARS-CoV-2 is primarily a pulmonary pathogen, renal and hepatic dysfunction are consistently described in patients with severe COVID-19 [4]. In one case series of patients with critical disease, >15% of the patients required continuous renal replacement therapy [6]. See the Acute Kidney Injury and Renal Replacement Therapy section for a more detailed discussion.

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

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

Interactions Between Drugs Used to Treat COVID-19 and Drugs Used to Treat Comorbidities
All ICU patients should be routinely monitored for drug-drug interactions. The potential for drug-drug interactions between investigational medications or medications used off-label to treat COVID-19 and concurrent drugs should be considered.
Sedation Management in Patients With COVID-19

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

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

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

The A-F Bundle also provides frontline staff with practical application strategies for each element [34]. The A-F Bundle should be incorporated using an interprofessional team model. This approach helps standardize communication among team members, improves survival, and reduces long-term cognitive dysfunction of patients [35]. Despite the known benefits of the A-F Bundle, its impact has not been directly assessed in patients with COVID-19; however, the use of the Bundle should be encouraged, when appropriate, to improve ICU patient outcomes. Prolonged mechanical ventilation of COVID-19 patients, coupled with deep sedation and potentially neuromuscular blockade, increases the workload of ICU staff. Additionally, significant drug shortages may force clinicians to use older sedatives with prolonged durations of action and active metabolites, impeding routine implementation of the PADIS Guidelines. This puts patients at additional risk for ICU and post-ICU complications.

Post-Intensive Care Syndrome

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

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

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

Other Intensive Care Unit-Related Complications

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

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

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

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

Acknowledgments

The Surviving Sepsis Campaign (SSC), an initiative supported by the SCCM 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 [1]. The COVID-19 Treatment Guidelines Panel (the Panel) has based the recommendations in this section on the SSC COVID-19 Guidelines with permission, and the Panel gratefully acknowledges the work of the SSC COVID-19 Guidelines Panel. The Panel also acknowledges the contributions and expertise of Andrew Rhodes, MBBS, MD, of St. George’s University Hospitals in London, England, and Waleed Alhazzani, MBBS, MSc, of McMaster University in Hamilton, Canada.

References


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

Last Updated: July 8, 2021

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

The doses listed here are for approved indications or from reported experiences or clinical trials.

<table>
<thead>
<tr>
<th>Dosing Regimens</th>
<th>Adult Doses</th>
<th>Pediatric Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remdesivir</td>
<td>Adults:</td>
<td>For Patients Who Are Not Mechanically Ventilated and/or on ECMO:</td>
</tr>
<tr>
<td></td>
<td>Same dose as for adults</td>
<td>RDV 200 mg IV on Day 1, then RDV 100 mg IV on Days 2–10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>For Patients Ages &lt;12 Years and Weighing &lt;40 kg:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RDV 3.5 mg/kg IV on Day 1, then RDV 2.5 mg/kg IV once daily starting on Day 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>For patients who are not mechanically ventilated and/or on ECMO, the duration is 5 days.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If patients have not shown clinical improvement after 5 days, treatment may be extended to up to 10 days.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>For mechanically ventilated patients and/or patients on ECMO, the recommended treatment duration is 10 days.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>For Patients Weighing &gt;12 Years and Weighing &gt;40 kg:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Same dose as for adults</td>
</tr>
</tbody>
</table>

### Adverse Events

- Nausea
- ALT and AST elevations
- Hypersensitivity
- Increases in prothrombin time
- Drug vehicle is SBECED, which has been associated with renal and liver toxicity. SBECED accumulation may occur in patients with moderate or severe renal impairment. Each 100 mg vial of RDV lyophilized powder contains 3 g of SBECED, and each 100 mg/20 mL vial of RDV solution contains 6 g of SBECED. Clinicians may consider preferentially using the lyophilized powder formulation (which contains less SBECED) in patients with renal impairment.

### Monitoring Parameters

- Infusion reactions
- Renal function and hepatic function should be monitored before and during treatment as clinically indicated.
- In the FDA product information, RDV is not recommended when eGFR is <30 mL/min. See the Remdesivir section for a discussion on using RDV in people with renal insufficiency.
- RDV may need to be discontinued if ALT level increases to >10 times ULN and should be discontinued if there is an increase in ALT level and signs or symptoms of liver inflammation are observed [1].
- Clinical drug-drug interaction studies of RDV have not been conducted.
- In vitro, RDV is a substrate of CYP3A4, OATP1B1, and P-gp and an inhibitor of CYP3A4, OATP1B1, OATP1B3, and MATE1 [1].
- Minimal to no reduction in RDV exposure is expected when RDV is coadministered with dexamethasone (Gilead Sciences, written communications, August 2020). CQ or HCQ may decrease the antiviral activity of RDV; coadministration of these drugs is not recommended [1].
- No significant interaction is expected between RDV and oseltamivir or baloxavir (Gilead Sciences, personal and written communications, August and September 2020).

### Drug-Drug Interaction Potential

- Monitor for potential AEs.
- Minor CYP3A4 substrate
- P-gp substrate
- Generally given on an empty stomach with water; however, administering IV RDV with food increases its bioavailability [2].
- A list of clinical trials is available here: Ivermectin

### Ivermectin

**Adults:**
- The dose most commonly used in clinical trials is IV 0.2–0.6 mg/kg PO given as a single dose or as a once-daily dose for up to 5 days.
- Generally well tolerated
- Dizziness
- Pruritis
- GI effects (e.g., nausea, diarrhea)
- Neurological AEs have been reported when IVM has been used to treat parasitic diseases, but it is not clear whether these AEs were caused by IVM or the underlying conditions.

**Pediatric Doses:**
- Doses reported in COVID-19 studies range from NTZ 500 mg PO 3 times daily to 4 times daily [3,4]. Higher doses are being studied (ClinicalTrials.gov Identifier NCT04744183).
- Doses used for antiprotozoal indications range from NTZ 500 mg to 1 g PO twice daily.
- Generally well tolerated
- Abdominal pain
- Headache
- Nausea
- Vomiting
- Urine discoloration
- Ocular discoloration (rare)
- Monitor for potential AEs.

### Nitazoxanide

**Adults:**
- Doses reported in COVID-19 studies range from NTZ 500 mg PO 3 times daily to 4 times daily [3,4]. Higher doses are being studied (ClinicalTrials.gov Identifier NCT04744183).
- Doses used for antiprotozoal indications range from NTZ 500 mg to 1 g PO twice daily.
- Generally well tolerated
- Monitor for potential AEs.

**Pediatric Doses:**
- NTZ should be taken with food.
- The oral suspension is not bioequivalent to the tablet formulation. A list of clinical trials is available here: Nitazoxanide

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**Note:**
- **AE** = adverse event; ALT = alanine transaminase; AST = aspartate aminotransferase; CQ = chloroquine; CYP = cytochrome P450; eGFR = estimated glomerular filtration rate. Use Authorization; FDA = Food and Drug Administration; GI = gastrointestinal; HCQ = hydroxychloroquine; IV = intravenous; IVM = ivermectin; LPV/R = lopinavir/ritonavir; MATE = multidrug and toxic extrusion protein; NTZ = nitazoxanide; OATP = organic anion transporter polypeptide; F; the Panel = the COVID-19 Treatment Guidelines Panel; P-gp = P-glycoprotein; PO = orally; RDV = remdesivir; SBECED = sulftoluretho-beta-cycloedrin; ULN = upper limit of normal.

**Key for Table 2e:**
- NTZ may be used in patients weighing >3.5 kg.
- ND = not delivered.
- A list of clinical trials is available here: Remdesivir

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**Notes:**
- Data from published literature and personal communications, August 2020. See the Remdesivir section for a discussion on using RDV in people with renal insufficiency.
- RDV should be administered in a hospital or a health care setting that can provide a similar level of care to an inpatient hospital.
- RDV is approved by the FDA for the treatment of COVID-19 in hospitalized adult and pediatric patients (aged ≥12 years and weighing ≥40 kg).
- An EUAb is available for hospitalized pediatric patients weighing 3.5 kg to <40 kg or aged <12 years and weighing ≥3.5 kg.
- A list of clinical trials is available here: Remdesivir
References


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

Last Updated: August 4, 2021

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

For dose modifications for patients with organ failure or those who require extracorporeal devices, please refer to product labels, when available.

There are currently not enough data to determine whether certain medications can be safely coadministered with therapies for the treatment of COVID-19. When using concomitant medications with similar toxicity profiles, consider performing additional safety monitoring.

The potential additive, antagonistic, or synergistic effects and the safety of using certain combination therapies for the treatment of COVID-19 are unknown. Clinicians are encouraged to report AEs to the FDA Medwatch program.

For the Panel’s recommendations for the drugs listed in this table, please refer to the drug-specific sections of the Guidelines and to Therapeutic Management of Hospitalized Adults With COVID-19.
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Adverse Events</th>
<th>Monitoring Parameters</th>
<th>Drug-Drug Interaction Potential</th>
<th>Comments and Links to Clinical Trials</th>
</tr>
</thead>
</table>
| Budesonide (Inhaled) | Dose for COVID-19 in Clinical Trials: Budesonide 800 mcg inhaled twice daily until symptom resolution or for up to 14 days[1,4]  | • Secondary infections  
• Oral thrush  
• Systemic adverse effects (less common)  | • Signs of adverse effects involving the oral mucosa or throat including thrush  
• Signs of systemic corticosteroid effects (e.g., adrenal suppression)  | • CYP3A4 substrate  
• Do not use with strong CYP3A4 inhibitors.  | • A list of clinical trials is available: Inhaled Budesonide                                                      |
| Dexamethasone (Systemic) | Dose for COVID-19: Dexamethasone 6 mg IV or PO once daily, for up to 10 days or until hospital discharge, whichever comes first[5]  | • Hyperglycemia  
• Secondary infections  
• Reactivation of latent infections (e.g., HBV, HSV, strongyloidiasis, TB)  
• Psychiatric disturbances  
• Avascular necrosis  
• Adrenal insufficiency  
• Increased blood pressure  
• Peripheral edema  
• Myopathy (particularly if used with neuromuscular blocking agents)[6,7]  | • Blood glucose  
• Blood pressure  
• Signs and symptoms of new infection  
• When initiating dexamethasone, consider appropriate screening and treatment to reduce the risk of Strongyloides hyperinfection in patients at high risk of strongyloidiasis or fulminant reactivation of HBV[6,8]  | • Moderate CYP3A4 inducer  
• CYP3A4 substrate  
• Although coadministration of RDV and dexamethasone has not been formally studied, a clinically significant PK interaction is not predicted (Gilead, written communication, August 2020).  | • If dexamethasone is not available, an alternative corticosteroid (e.g., prednisone, methylprednisolone, hydrocortisone) can be used.  
• The approximate total daily dose equivalencies for these glucocorticoids to dexamethasone 6 mg (PO or IV) are: prednisone 40 mg, methylprednisolone 32 mg, and hydrocortisone 160 mg.  
• A list of clinical trials is available: Dexamethasone                                                      |
| Fluvoxamine     | Dose for COVID-19 in Clinical Trials: Various dosing regimens used  | • Nausea  
• Diarrhea  
• Dyspepsia  
• Asthenia  
• Insomnia  
• Somnolence  
• Sweating  
• Suicidal ideation (rare)  | • Hepatic function  
• Drug interactions  
• Monitor for withdrawal symptoms when tapering dose.  | • CYP2D6 substrate  
• Fluvoxamine inhibits several CYP450 isoenzymes (CYP1A2, CYP2C9, CYP3A4, CYP2C19, CYP2D6).  
• Deadministration of trazodone, trazodone, alprazolam, or pimozide with fluvoxamine is contraindicated.  | • Fluvoxamine may enhance anticoagulant effects of antithrombotics and anticoagulants; consider additional monitoring when these drugs are used concomitantly with fluvoxamine.  
• The use of MAOIs concomitantly with fluvoxamine or within 14 days of treatment with fluvoxamine is contraindicated.  
• A list of clinical trials is available: Fluvoxamine                                                      |
| Granulocyte-Macrophage Colony-Stimulating Factor Inhibitors | Dose for COVID-19 in Clinical Trials:  | • No treatment emergent SAEs were reported in clinical trials.  | • CBC with differential  
• Liver enzymes  
• Infusion reactions  
• HSR  | • Data not available  | • A list of clinical trials is available: Lenzilumab  |
| Lenzilumab      | Lenzilumab 600 mg times 3 doses, administered 8 hours apart by IV infusion over 1 hour[9]  |  |  |  |  |
| Mavrilumab      | Mavrilumab 6 mg/kg IV infusion once[10]  | • No treatment emergent SAEs were reported in clinical trials.  | • CBC with differential  
• Liver enzymes  
• Infusion reactions  
• HSR  | • Data not available  | • A list of clinical trials is available: Mavrilumab  |
| Otilimab        | Otilimab 90 mg IV infusion once[11]  | • No treatment emergent SAEs were reported in clinical trials.  | • CBC with differential  
• Liver enzymes  
• Infusion reactions  
• HSR  | • Data not available  | • A list of clinical trials is available: Otilimab  |
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
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<tbody>
<tr>
<td><strong>Interferon</strong></td>
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<tr>
<td>Interferon Alfa</td>
<td>Peg-IFN Alfa-2a &lt;br&gt; Dose for MERS: Peg-IFN alfa-2a 180 μg SQ once weekly for 2 weeks</td>
<td>• Flu-like symptoms &lt;br&gt; • Injection site reactions &lt;br&gt; • Liver function abnormalities &lt;br&gt; • Decreased blood counts &lt;br&gt; • Worsening depression &lt;br&gt; • Insomnia &lt;br&gt; • Nausea &lt;br&gt; • Vomiting &lt;br&gt; • HTN &lt;br&gt; • Induction of autoimmunity</td>
<td>CBC with differential &lt;br&gt; • Liver enzymes; avoid use if Child-Pugh Score &gt;6. &lt;br&gt; • Renal function: reduce dose if CrCl &lt;30 ml/min.</td>
<td>Low potential for drug-drug interactions &lt;br&gt; • Inhibition of CYP1A2</td>
<td>For COVID-19, IFN alfa has primarily been used as rebalancing and usually as part of a combination regimen. &lt;br&gt; <strong>Use with caution</strong> with other hepatotoxic agents. &lt;br&gt; <strong>Reduce dose if ALT &gt;5 times ULN.</strong> Discontinue if bilirubin level also increases. &lt;br&gt; <strong>Reduce dose or discontinue in severe neutropenia or thrombocytopenia or neutropenia and thrombocytopenia occur.</strong> &lt;br&gt; A list of clinical trials is available: <a href="http://med-expert.com.ua">Interferon</a> &lt;br&gt; **Availability:**新产品</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Dosing Regimen</td>
<td>Adverse Events</td>
<td>Drug-Drug Interaction Potential</td>
<td>Comments and Links to Clinical Trials</td>
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<tr>
<td><strong>Tocilizumab</strong></td>
<td><strong>Dose for COVID-19 in Clinical Trial:</strong> Single dose of tocilizumab 8 mg/kg actual body weight IV. <strong>Dose should not exceed 800 mg.</strong> Administer in combination with dexamethasone.</td>
<td>• Infusion-related reactions • HSR • GI perforation • Hepatotoxicity • Treatment-related changes on laboratory tests for neutrophils, platelets, lipids, and liver enzymes • HIV reactivation • IL-6 • Infusion reactions • Neutrophils • Platelets • Liver enzymes • Cases of severe and disseminated strongyloidiasis have been reported with the use of tocilizumab and corticosteroids in patients with COVID-19. Prophylactic treatment with VM should be considered for persons who are from areas where strongyloidiasis is endemic. <strong>Elevated IL-6 may downregulate CYP enzymes; use of tocilizumab may lead to increased metabolism of drugs that are CYP450 substrates.</strong> Effects on CYP450 may persist for weeks after therapy.</td>
<td>Tocilizumab use should be avoided in patients who are significantly immunocompromised. The safety of using tocilizumab plus a corticosteroid in immunocompromised patients is unknown. Treatment with tocilizumab may mask signs of acute inflammation or infection (i.e., by suppressing fever and CRP levels). The SG formulation of tocilizumab is not intended for IV administration. A list of clinical trials is available: Tocilizumab.</td>
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</tr>
<tr>
<td><strong>Siltuximab</strong></td>
<td><strong>Dose for Multicentric Castleman Disease:</strong> Siltuximab 11 mg/kg administered over 1 hour by IV infusion every 3 weeks. <strong>Dose for COVID-19:</strong> Dose and duration unknown</td>
<td>• Infusion-related reactions • HSR • GI perforation • Neutropenia • HTN • Dizziness • Rash • Pruritus • Hypertension</td>
<td>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.</td>
<td>Treatment with siltuximab may mask signs of acute inflammation or infection (i.e., by suppressing fever and CRP levels). A list of clinical trials is available: Siltuximab.</td>
<td></td>
</tr>
<tr>
<td><strong>Acalabrutinib</strong></td>
<td><strong>Dose for FDA-Approved Indications:</strong> Acalabrutinib 100 mg PO every 12 hours <strong>Dose for COVID-19:</strong> Dose and duration unknown</td>
<td>• Hemorrhage • Cytopenias (neutropenia, anemia, thrombocytopenia, lymphopenia) • Atrial fibrillation and flutter • Infection • Headache • Diarrhea • Fatigue • Myalgia • CBC with differential • Signs and symptoms of bleeding (particularly when coadministered with an anticoagulant or antiplatelet therapy) • Cardiac arhythmias • New infections</td>
<td>Avoid concurrent use with strong CYP3A4 inhibitors or inducers. Dose reduction may be necessary with moderate CYP3A4 inhibitors. Avoid concurrent PPI use. HR-β-receptor antagonist should be administered 2 hours after acalabrutinib.</td>
<td>Avoid use in patients with severe hepatic impairment. Patients with underlying cardiac risk factors, hypertension, or acute infections may be predisposed to atrial fibrillation. A list of clinical trials is available: Acalabrutinib.</td>
<td></td>
</tr>
<tr>
<td><strong>Ibrutinib</strong></td>
<td><strong>Dose for FDA-Approved Indications:</strong> Ibrutinib 420 mg or 560 mg PO once daily <strong>Dose for COVID-19:</strong> Dose and duration unknown</td>
<td>• Hemorrhage • Cardiac arhythmias • Serious infections • Cytopenias (thrombocytopenia, neutropenia, anemia) • HTN • Diarrhea • Musculoskeletal pain • Rash • CBC with differential • Blood pressure • Signs and symptoms of bleeding (particularly when coadministered with an antiplatelet drug) • Cardiac arhythmias • New infections</td>
<td>Avoid concurrent use with strong CYP3A inhibitors or inducers. Dose reduction may be necessary with moderate CYP3A4 inhibitors.</td>
<td>Avoid use in patients with severe baseline hepatic impairment. Dose modifications required in patients with mild or moderate hepatic impairment. Patients with underlying cardiac risk factors, HTN, or acute infections may be predisposed to cardiac arhythmias. A list of clinical trials is available: Ibrutinib.</td>
<td></td>
</tr>
<tr>
<td>Drug Name</td>
<td>Dosing Regimen</td>
<td>Adverse Events</td>
<td>Monitoring Parameters</td>
<td>Drug-Drug Interaction Potential</td>
<td>Comments and Links to Clinical Trials</td>
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</tbody>
</table>
| **Zanubrutinib** | Dose for FDA-Approved Indications:  
- Zanubrutinib 160 mg PO twice daily or 320 mg PO once daily  
Dose for COVID-19:  
- Dose and duration unknown | • Hemorrhage  
- Cytopenias (neutropenia, thrombocytopenia, anemia, leukopenia)  
- Atrial fibrillation and flutter  
- Infection  
- Rash  
- Bruising  
- Diarrhea  
- Cough  
- Musculoskeletal pain | CBC with differential  
- Signs and symptoms of bleeding  
- Cardiac arrhythmias  
- New infections | • Avoid concomitant use with moderate or strong CYP3A4 inhibitors.  
• Dose reduction required in patients with severe hepatic impairment.  
• A list of clinical trials is available: [Zanubrutinib](#) |
| **Baricitinib** | For Adults and Children Aged ≥9 Years Based on eGFR:  
- eGFR ≥60 mL/min/1.73 m²:  
  - Baricitinib 4 mg PO once daily  
- eGFR 30 to <60 mL/min/1.73 m²:  
  - Baricitinib 2 mg PO once daily  
- eGFR 15 to <30 mL/min/1.73 m²:  
  - Baricitinib 1 mg PO once daily  
- eGFR <15 mL/min/1.73 m²:  
  - Not recommended | • Lymphoma and other malignancies  
• Thrombosis  
• GI perforation  
• Treatment-related changes in lymphocytes, neutrophils, Hgb, liver enzymes  
• HSV reactivation  
• Herpes zoster | CBC with differential  
• Renal function  
• Liver enzymes  
• New infections | • Dose modification is recommended when concurrently administering a strong CYP3A4 inhibitor.  
• Avoid concomitant administration of live vaccines.  
• Baricitinib is available through an FDA EUA. See the EUA for dosing guidance for patients with:  
  - ALC <200 cells/µL  
  - ANC <500 cells/µL  
  - If increases in ALT or AST are observed and DILI is suspected, interrupt baricitinib treatment until the diagnosis of DILI is excluded. |
| **Ruxolitinib** | For Children Aged 2 to <9 Years Based on eGFR:  
- eGFR ≥60 mL/min/1.73 m²:  
  - Baricitinib 2 mg PO once daily  
- eGFR 30 to <60 mL/min/1.73 m²:  
  - Baricitinib 1 mg PO once daily  
- eGFR <30 mL/min/1.73 m²:  
  - Not recommended  
Duration of Therapy:  
- For up to 14 days or until hospital discharge | Thrombocytopenia  
• Anemia  
• Neutropenia  
• Liver enzyme elevations  
• Risk of infection  
• Dizziness  
• Headache  
• Diarrhea  
• CPK elevation  
• Herpes zoster | CBC with differential  
• Liver enzymes  
• New infections | • Dose modifications required when administered with strong CYP3A4 inhibitors.  
• Avoid use with doses of fluconazole >200 mg.  
• Dose modification may be required in patients with hepatic impairment, moderate or severe renal impairment, or thrombocytopenia.  
• A list of clinical trials is available: [Ruxolitinib](#) |
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Adverse Events</th>
<th>Monitoring Parameters</th>
<th>Drug-Drug Interaction Potential</th>
<th>Comments and Links to Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tofacitinib</td>
<td>Dose for FDA-Approved indications: • Tofacitinib 5 mg PO twice daily for rheumatoid and psoriatic arthritis</td>
<td>• Thrombotic events (pulmonary embolism, DVT, arterial thrombosis) • Anemia • Risk of infection • GI perforation • Diarrhea • Headache • Herpes zoster • Lipid elevations • Liver enzyme elevations • Lymphoma and other malignancies</td>
<td>• CBC with differential • Liver enzymes • New infections</td>
<td>• Dose modifications required when administered with strong CYP3A4 inhibitors or when used with a moderate CYP3A4 inhibitor that is coadministered with a strong CYP2C19 inhibitor. • Avoid administration of live vaccines.</td>
<td>• Avoid use in patients with ALC &lt;500 cells/μL, ANC &lt;1,000 cells/μL, or Hgb &lt;9 grams/dL. • Dose modification may be required in patients with moderate or severe renal impairment or moderate hepatic impairment. • A list of clinical trials is available: Tofacitinib</td>
</tr>
<tr>
<td>Non-SARS-CoV-2 Specific Immunoglobin</td>
<td>Dose varies based on indication and formulation.</td>
<td>Allergic reactions, including anaphylaxis • Renal failure • Thrombotic events • Aseptic meningitis syndrome • Hemolysis • TRALI • Transmission of infectious pathogens • AEs may vary by formulation. • AEs may be increased with high-dose, rapid infusion, or in patients with underlying conditions.</td>
<td>• Transfusion-related reactions • Vital signs at baseline and during and after infusion • Renal function. Discontinue treatment if function deteriorates.</td>
<td>• IVIG may interfere with immune response to certain vaccines.</td>
<td>• A list of clinical trials is available: Inhaled budesonide in the treatment of early COVID-19 (STOIC): a Phase 2, open-label, randomised controlled trial. Lancet Respir Med. 2021. Available at: <a href="https://www.ncbi.nlm.nih.gov/pubmed/33844996">https://www.ncbi.nlm.nih.gov/pubmed/33844996</a>.</td>
</tr>
</tbody>
</table>

Key: AE = adverse event; ALC = absolute lymphocyte count; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CBC = complete blood count; CHF = congestive heart failure; CPK = creatine phosphokinase; CrCl = creatinine clearance; CRP = C-reactive protein; CYP = cytochrome P; DILI = drug induced liver injury; DVT = deep vein thrombosis; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; GI = gastrointestinal; HBV = hepatitis B; Hgb = hemoglobin; HSR = hypersensitivity reaction; HSV = herpes simplex virus; HTN = hypertension; IFN = interferon; IL = interleukin; IMV = invasive mechanical ventilation; IV = intravenous; IVIG = intravenous immunoglobulin; IVM = ivermectin; MAOI = monoamine oxidase inhibitor; MERS = Middle East respiratory syndrome; OAT = organic anion transporter; the Panel = the COVID-19 Treatment Guidelines Panel; Peg-IFN = pegylated interferon; P-gp = P-glycoprotein; PK = pharmacokinetic; PO = orally; PPI = proton pump inhibitor; RDV = remdesivir; SAE = serious adverse event; SQ = subcutaneous; TB = tuberculosis; TNF = tumor necrosis factor; TRALI = transfusion-related acute lung injury; ULN = upper limit of normal |

References


<...>
Правила подаці та оформлення статей

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ПУБЛІКАЦІЯ БЕЗКОШТОВНА

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