Clinical Management Summary

Last Updated: February 1, 2022

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.
For a list of risk factors, see the CDC webpage [Underlying Medical Conditions Associated With Higher Risk for Severe COVID-19](https://www.cdc.gov/coronavirus/2019-ncov/need-extra-care/c certain-medical-conditions.html) and the Patient Prioritization for Treatment section below.

Ritonavir-boosted nirmatrelvir has significant drug-drug interactions. Clinicians should carefully review a patient’s concomitant medications and evaluate potential drug-drug interactions.

If a patient requires hospitalization after starting treatment, the full treatment course can be completed at the health care provider’s discretion.

The B.1.1.529 (Omicron) VOC is currently the dominant SARS-CoV-2 variant in the United States. Sotrovimab is the only anti-SARS-CoV-2 mAb that is active against the Omicron VOC.

Administration of remdesivir requires 3 consecutive days of IV infusion.

Molnupiravir has a lower efficacy than the other treatment options. Therefore, it should be used **ONLY** when the other options are not available or feasible.
There is currently a lack of safety and efficacy data on the use of these agents in outpatients with COVID-19; using systemic glucocorticoids in this setting may cause harm.

These individuals should receive oximetry monitoring and close follow-up through telehealth, visiting nurse services, or in-person visits.

Provide an advanced level of home care, including supplemental oxygen (whether patients are receiving oxygen for the first time or are increasing their baseline oxygen requirements), pulse oximetry, laboratory monitoring, and close follow-up through visiting nurse services, telehealth, or in-person visits.

See Therapeutic Management of Hospitalized Adults With COVID-19.

Key: AE = adverse events; CDC = Centers for Disease Control and Prevention; ED = emergency department; IV = intravenous; mAb = monoclonal antibody; the Panel = the COVID-19 Treatment Guidelines Panel; PO = orally; VOC = variant of concern
Figure 2. Therapeutic Management of Hospitalized Adults With COVID-19 Based on Disease Severity

<table>
<thead>
<tr>
<th>DISEASE SEVERITY</th>
<th>PANEL’S RECOMMENDATIONS</th>
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</table>
| Hospitalized but Does Not Require Supplemental Oxygen | The Panel **recommends against** the use of dexamethasone (AIIa) or other corticosteroids (AII).\(^a\)  
There is insufficient evidence to recommend either for or against the routine use of remdesivir. For patients at high risk of disease progression, remdesivir may be appropriate. |
| Hospitalized and Requires Supplemental Oxygen        | Use 1 of the following options:  
\- **Remdesivir**\(^b\,\,^c\) (e.g., for patients who require minimal supplemental oxygen) (BIIa)  
\- **Dexamethasone plus remdesivir**\(^b\,\,^c\) (BIIb)  
\- **Dexamethasone** (BII)  
For patients on dexamethasone with rapidly increasing oxygen needs and systemic inflammation, add a second immunomodulatory drug\(^d\) (e.g., baricitinib\(^b\) or tocilizumab\(^b\)) (CIIa). |
| Hospitalized and Requires Oxygen Through a High-Flow Device or NIV | Use 1 of the following options:  
\- **Dexamethasone** (AI)  
\- **Dexamethasone plus remdesivir**\(^c\) (BIII)  
For patients with rapidly increasing oxygen needs and systemic inflammation, add either baricitinib\(^b\) (BIIa) or IV tocilizumab\(^b\) (BIIa) to 1 of the 2 options above.\(^e\,\,^f\) |
| Hospitalized and Requires MV or ECMO                 | **Dexamethasone** (AI)\(^g\)  
For patients who are within 24 hours of admission to the ICU:  
\- **Dexamethasone plus IV tocilizumab** (BIIa)  
If IV tocilizumab is not available or not feasible to use, IV sarilumab can be used (BIIa). |

**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

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\(^a\) Corticosteroids prescribed for an underlying condition should be continued.  
\(^b\) If the patient progresses to requiring high-flow oxygen, NIV, MV, or ECMO, complete the full course of remdesivir (refer to Table A).  
\(^c\) Evidence suggests that the benefit of remdesivir is greatest when the drug is given early in the course of COVID-19 (e.g., within 10 days of symptom onset). Clinical trials have not demonstrated a mortality benefit for remdesivir, but a large placebo-controlled trial showed that remdesivir reduced time to clinical recovery in hospitalized patients. See Rationale for the Use of Remdesivir below.  
\(^d\) Drugs are listed alphabetically. There are no studies directly comparing baricitinib and tocilizumab, and there is insufficient evidence to recommend 1 drug or 1 class of drug (i.e., JAK inhibitors, anti-IL-6 receptor mAbs) over the other. Treatment decisions should be based on local guidance, drug availability, and patient comorbidities.  
\(^e\) If baricitinib and IV tocilizumab are not available or not feasible to use, **tocilizumab** can be used instead of baricitinib (BIIa) and **sarilumab** can be used instead of IV tocilizumab (BIIa).  
\(^f\) The Panel **recommends against** the use of **baricitinib** in combination with **tocilizumab** for the treatment of COVID-19, except in a clinical trial (AIII). Because both baricitinib and tocilizumab are potent immunsuppressants, there is the potential for an additive risk of infection.  
\(^g\) The combination of **dexamethasone plus remdesivir** may be considered for patients who have recently been intubated (CIII). The Panel **recommends against** the use of **remdesivir** monotherapy in these patients (AIIa).  

**Key:** ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; IL = interleukin; IV = intravenous; JAK = Janus kinase; mAb = monoclonal antibody; MV = mechanical ventilation; NIV = noninvasive ventilation; the Panel = the COVID-19 Treatment Guidelines Panel; PO = orally
**General Management of Nonhospitalized Patients With Acute COVID-19**

*Last Updated: December 16, 2021*

<table>
<thead>
<tr>
<th>Summary Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Management of nonhospitalized patients with acute COVID-19 should include providing supportive care, considering the use of COVID-19-specific therapy for patients who have a high risk for disease progression, 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).</td>
</tr>
<tr>
<td>• When possible, patients with symptoms of COVID-19 should be triaged via telehealth visits to determine whether they require COVID-19-specific therapy and in-person care (AIII).</td>
</tr>
<tr>
<td>• 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).</td>
</tr>
<tr>
<td>• 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).</td>
</tr>
<tr>
<td>• See <a href="https://www.covid19treatmentguidelines.nih.gov/">Therapeutic Management of Nonhospitalized Adults With COVID-19</a> for specific recommendations on using pharmacologic therapy in nonhospitalized patients.</td>
</tr>
</tbody>
</table>

**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional  
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**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](https://www.covid19treatmentguidelines.nih.gov/). 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. 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. 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). When managing outpatients with COVID-19, clinicians should provide supportive care, take steps to reduce the risk of SARS-CoV-2 transmission (e.g., wear a mask, isolate the patient),⁴,⁵ evaluate the need for COVID-19-specific therapy, and advise 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 symptoms of COVID-19 should be triaged via telehealth visits to determine whether they require COVID-19-specific therapy and in-person care (AIIII). 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 (AIIII).

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 (AIIII). 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 conditions that are associated with a risk of progression to severe COVID-19. The individual who performs the initial triage should use their clinical judgement to determine whether a patient requires ambulance transport. There are unique considerations for residents of nursing homes and other long-term care facilities who develop acute COVID-19. Decisions about transferring these patients for an in-person evaluation should be a collaborative effort between the resident (or their health care decision maker), a hospital-based specialist (e.g., an emergency physician or geriatrician), and the clinical manager of the facility.⁹

In some settings where clinical evaluation is challenged by geography, health care provider home visits may be used to evaluate patients.¹⁰ Patients who are homeless should be provided with housing where they can adequately self-isolate. Providers should be aware of the potential adverse effects of prolonged social isolation, including depression and anxiety.⁷ All outpatients should receive instructions regarding self-care, isolation, and follow-up, and should be advised to contact a health care provider or a local ED for any worsening symptoms.¹¹,¹² Guidance for implementing home care and isolation of outpatients with COVID-19 is provided by the U.S. Centers for Disease Control and Prevention.
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 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. 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. 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, SpO\textsubscript{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. Additionally, SpO\textsubscript{2} readings obtained through a mobile phone application may not be accurate enough for clinical use. 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.\textsuperscript{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 that allows 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 a 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. 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, SpO\textsubscript{2} 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. In general, there are no changes to fetal monitoring recommendations in the outpatient setting, and fetal management should be similar to the fetal management used for other pregnant patients with medical illness. 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 1 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.

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**


16. Jordan TB, Meyers CL, Schrading WA, Donnelly JP. The utility of iPhone oximetry apps: a comparison with


Several therapeutic options are now available for the treatment of nonhospitalized adults with mild to moderate COVID-19 who are at high risk of disease progression. A number of factors may affect the selection of the best treatment option for a specific patient. These factors include the clinical efficacy and availability of the treatment option, the feasibility of administering parenteral medications (i.e., sotrovimab or remdesivir), the potential for significant drug-drug interactions (e.g., those associated with the use of ritonavir-boosted nirmatrelvir [Paxlovid]), and the regional prevalence of variants of concern (VOC).

Figure 1 outlines the COVID-19 Treatment Guidelines Panel’s (the Panel) recommendations for using these therapeutic interventions outside the hospital inpatient setting.

**Figure 1. Therapeutic Management of Nonhospitalized Adults With COVID-19**

<table>
<thead>
<tr>
<th>PATIENT DISPOSITION</th>
<th>PANEL’S RECOMMENDATIONS</th>
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| Does Not Require Hospitalization or Supplemental Oxygen | All patients should be offered symptomatic management (AIII). For patients who are at high risk of progressing to severe COVID-19⁹ (treatments are listed in order of preference based on efficacy and convenience of use):  
  - Ritonavir-boosted nirmatrelvir (Paxlovid)⁶⁻⁷ (Alla)  
  - Sotrovimab¹ (Alla)  
  - Remdesivir⁷⁻⁸ (BIIa)  
  - Molnupiravir⁶⁻⁷ (CIIa)  
  The Panel recommends against the use of dexamethasone or other systemic corticosteroids in the absence of another indication (AIII).⁹ |
| Discharged From Hospital Inpatient Setting in Stable Condition and Does Not Require Supplemental Oxygen | The Panel recommends against continuing the use of remdesivir (Alla), dexamethasone⁹ (Alla), or baricitinib⁴ (Alla) after hospital discharge. |
| Discharged From Hospital Inpatient Setting and Requires Supplemental Oxygen  
  For those who are stable enough for discharge but who still require oxygen⁴  
  | There is insufficient evidence to recommend either for or against the continued use of remdesivir or dexamethasone. |
| Discharged From ED Despite New or Increasing Need for Supplemental Oxygen  
  When hospital resources are limited, inpatient admission is not possible, and close follow-up is ensured  
  | The Panel recommends using dexamethasone 6 mg PO once daily for the duration of supplemental oxygen (dexamethasone use should not exceed 10 days) with careful monitoring for AEs (BIII).  
  Since remdesivir is recommended for patients with similar oxygen needs who are hospitalized,¹ clinicians may consider using it in this setting. Given that remdesivir requires IV infusions for up to 5 consecutive days, there may be logistical constraints to administering remdesivir in the outpatient setting. |

**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; IIIb = Nonrandomized trials or observational cohort studies; III = Expert opinion
For a list of risk factors, see the CDC webpage Underlying Medical Conditions Associated With Higher Risk for Severe COVID-19 and the Patient Prioritization for Treatment section below.

Ritonavir-boosted nirmatrelvir has significant drug-drug interactions. Clinicians should carefully review a patient’s concomitant medications and evaluate potential drug-drug interactions.

If a patient requires hospitalization after starting treatment, the full treatment course can be completed at the health care provider’s discretion.

The B.1.1.529 (Omicron) VOC is currently the dominant SARS-CoV-2 variant in the United States. Sotrovimab is the only anti-SARS-CoV-2 mAb that is active against the Omicron VOC.

Administration of remdesivir requires 3 consecutive days of IV infusion.

Molnupiravir has a lower efficacy than the other treatment options. Therefore, it should be used ONLY when the other options are not available or feasible.

There is currently a lack of safety and efficacy data on the use of these agents in outpatients with COVID-19; using systemic glucocorticoids in this setting may cause harm.

These individuals should receive oximetry monitoring and close follow-up through telehealth, visiting nurse services, or in-person visits.

Provide an advanced level of home care, including supplemental oxygen (whether patients are receiving oxygen for the first time or are increasing their baseline oxygen requirements), pulse oximetry, laboratory monitoring, and close follow-up through visiting nurse services, telehealth, or in-person visits.

See Therapeutic Management of Hospitalized Adults With COVID-19.

Key: AE = adverse events; CDC = Centers for Disease Control and Prevention; ED = emergency department; IV = intravenous; mAb = monoclonal antibody; the Panel = the COVID-19 Treatment Guidelines Panel; PO = orally; VOC = variant of concern

Patient Prioritization for Treatment

During surges in cases of SARS-CoV-2 infection, logistical or supply constraints may make it impossible to offer available therapeutics to all the nonhospitalized patients who are eligible to receive them. In these situations, the Panel recommends prioritizing the treatment of patients who are at the highest risk of clinical progression.

In Table A, the Panel has prioritized the risk groups for anti-SARS-CoV-2 therapy based on 4 key elements: age, vaccination status, immune status, and the presence of risk factors for clinical progression. The groups are listed in descending order of priority. For a list of risk factors, see the Centers for Disease Control and Prevention (CDC) website Underlying Medical Conditions Associated With Higher Risk for Severe COVID-19.

Table A. Patient Risk Groups for Prioritizing the Use of Anti-SARS-CoV-2 Therapy

<table>
<thead>
<tr>
<th>Tier</th>
<th>Risk Groups</th>
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| 1    | • Immunocompromised individuals who are not expected to mount an adequate immune response to COVID-19 vaccination or SARS-CoV-2 infection due to their underlying conditions, regardless of their vaccine status (see Immunocompromising Conditions below); or  
• Unvaccinated individuals who are at the highest risk of severe disease (anyone aged ≥75 years or anyone aged ≥65 years with additional risk factors) |
| 2    | • Unvaccinated individuals who are at risk of severe disease and who are not included in Tier 1 (anyone aged ≥65 years or anyone aged <65 years with clinical risk factors) |
| 3    | • Vaccinated individuals who are at high risk of severe disease (anyone aged ≥75 years or anyone aged ≥65 years with clinical risk factors)  
• Vaccinated individuals who have not received a COVID-19 vaccine booster dose are likely to be at higher risk for severe disease; patients who have not received a booster dose and who are within this tier should be prioritized for treatment. |
Immunocompromising Conditions

The CDC website [COVID-19 Vaccines for Moderately or Severely Immunocompromised People](https://www.cdc.gov/coronavirus/2019-ncov/vaccination/high-risk.html) provides a list of moderate and severe immunocompromising conditions.

If these anti-SARS-CoV-2 agents cannot be provided to all moderately to severely immunocompromised individuals because of logistical constraints or supply limitations, the Panel suggests prioritizing their use for those who are least likely to mount an adequate response to COVID-19 vaccination or SARS-CoV-2 infection and who are at risk for severe outcomes. This includes:

- Patients who are within 1 year of receiving B cell-depleting therapies (e.g., rituximab, ocrelizumab, ofatumumab, alemtuzumab)
- Patients who are receiving Bruton tyrosine kinase inhibitors
- Chimeric antigen receptor T cell recipients
- Post-hematopoietic cell transplant recipients who have chronic graft versus host disease or who are taking immunosuppressive medications for another indication
- Patients with hematologic malignancies who are on active therapy
- Lung transplant recipients
- Patients who are within 1 year of receiving a solid organ transplant (other than a lung transplant)
- Solid organ transplant recipients with recent treatment for acute rejection with T cell- or B cell-depleting agents
- Patients with severe combined immunodeficiencies
- Patients with untreated HIV who have a CD4 T lymphocyte cell count <50 cells/mm$^3$

If supplies are extremely limited, the Panel suggests prioritizing those who are more severely immunocompromised (based on the list above) and who have additional risk factors for severe disease.

### Table B. Dosing Regimens for the Drugs Recommended for High-Risk, Nonhospitalized Adults With Mild to Moderate COVID-19, Listed in Order of Preference Based on Efficacy and Convenience of Use

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Time From Symptom Onset$^a$</th>
</tr>
</thead>
</table>
| Ritonavir-Boosted Nirmatrelvir (Paxlovid) | **eGFR ≥60 mL/min:**  
Nirmatrelvir 300 mg with RTV 100 mg PO twice daily for 5 days  
**eGFR 30 to <60 mL/min:**  
Nirmatrelvir 150 mg with RTV 100 mg PO twice daily  
**eGFR <30 mL/min:**  
Not recommended  
Severe Hepatic Impairment (Child-Pugh Class C):  
Not recommended | ≤5 days |
a Per EUA criteria or clinical trial entry criteria.

b An eGFR <30 mL/min at screening or <90 days before screening was considered an exclusion criterion in the outpatient RDV study PINETREE, but only if a participant’s weight was <48 kg. See the Remdesivir section for a discussion of RDV use in patients with renal impairment.

c If RDV is administered to patients who have a new or increasing need for supplemental oxygen but who are discharged from the ED because hospital resources are limited and inpatient admission is not possible, the total duration of therapy is ≤5 days.

Key: ED = emergency department; eGFR = estimated glomerular filtration rate; EUA = Emergency Use Authorization; IV = intravenous; PO = orally; RDV = remdesivir; RTV = ritonavir; SOT = sotrovimab

### Symptom Management

Symptomatic treatment includes using over-the-counter antipyretics, analgesics, or antitussives for fever, headache, myalgias, and cough. Patients with dyspnea may benefit from resting in the prone position rather than the supine position.¹ Health care providers should consider educating patients about breathing exercises, as severe breathlessness may cause anxiety.² Patients should be advised to drink fluids regularly to avoid dehydration. Rest is recommended as needed during the acute phase of COVID-19, and ambulation and other forms of activity should be increased according to the patient’s tolerance. Patients should be educated about the variability in time to symptom resolution and complete recovery.

### Rationale for the Use of Specific Agents Listed in Figure 1

The Panel’s recommendations and preferences for the therapeutics that are used to treat nonhospitalized patients with COVID-19 are based on the results of clinical trials for ritonavir-boosted nirmatrelvir, remdesivir, and molnupiravir, and on the results of clinical trials and laboratory assessments of the activity of the anti-SARS-CoV-2 monoclonal antibody (mAb) products that are currently available through Emergency Use Authorizations (EUAs) from the Food and Drug Administration (FDA) for the treatment of COVID-19. These therapies are recommended for patients with mild to moderate COVID-19 who are at high risk of progressing to severe disease.

It should be noted that a number of factors affect the selection of the best treatment option for a specific patient. These factors include the clinical efficacy and the availability of the treatment option, the feasibility of administering parenteral medications (i.e., sotrovimab, remdesivir), and the potential for significant drug-drug interactions (i.e., the interactions associated with using ritonavir-boosted nirmatrelvir).

The Panel favors the use of ritonavir-boosted nirmatrelvir in most high-risk, nonhospitalized patients with mild to moderate COVID-19. If ritonavir-boosted nirmatrelvir is not available or cannot be used because of drug interactions, the Panel recommends using the anti-SARS-CoV-2 mAb sotrovimab as the second option. If sotrovimab is not available, then the Panel recommends using remdesivir. Molnupiravir should ONLY be used when the other 3 options are either not available or cannot be used.

There are currently no clinical trial data that directly compare the clinical efficacy of these 4 therapies,
and there are no data on the use of combinations of antiviral agents and/or anti-SARS-CoV-2 mAbs for the treatment of COVID-19. The rationale for each of the Panel’s recommendations is discussed below.

**Ritonavir-Boosted Nirmatrelvir (Paxlovid)**

Nirmatrelvir is an orally bioavailable protease inhibitor that is active against M\(^{\text{PRO}}\), a viral protease that plays an essential role in viral replication by cleaving the 2 viral polyproteins.\(^3\) It has demonstrated antiviral activity against all coronaviruses that are known to infect humans.\(^4\) Nirmatrelvir is packaged with ritonavir (as Paxlovid), a strong cytochrome P450 3A4 inhibitor and pharmacokinetic boosting agent. Ritonavir is required to increase nirmatrelvir concentrations to the target therapeutic ranges.

**Recommendation**

- The Panel recommends using **nirmatrelvir 300 mg with ritonavir 100 mg (Paxlovid)** orally (PO) twice daily for 5 days in those aged \(\geq 12\) years and weighing \(\geq 40\) kg; treatment should be initiated as soon as possible and within 5 days of symptom onset (AI\(\text{l}\)a).
- Ritonavir-boosted nirmatrelvir has significant and complex drug-drug interactions, primarily due to the ritonavir component of the combination.
- Before prescribing ritonavir-boosted nirmatrelvir, clinicians should carefully review the patient’s concomitant medications, including over-the-counter medications and herbal supplements, to evaluate potential drug-drug interactions.
- The EUA fact sheet for ritonavir-boosted nirmatrelvir and the Liverpool COVID-19 Drug Interactions website should be utilized to identify and manage drug-drug interactions. A quick reference guide is also provided in the Panel’s statement on the drug-drug interactions for ritonavir-boosted nirmatrelvir.

In the EPIC-HR trial, ritonavir-boosted nirmatrelvir reduced the risk of hospitalization or death by 88% compared to placebo in nonhospitalized adults with laboratory-confirmed SARS-CoV-2 infection.\(^5\) This efficacy is comparable to the efficacies reported in similar patient populations for sotrovimab (85% relative reduction),\(^6\) and remdesivir (87% relative reduction),\(^7\) and greater than the efficacy reported for molnupiravir in this setting (30% relative reduction).\(^8\)

Ritonavir-boosted nirmatrelvir is expected to be active against the B.1.1.529 (Omicron) VOC, although clinical efficacy data are lacking.\(^9\)\(^,\)\(^11\) Because ritonavir-boosted nirmatrelvir has the potential for significant drug-drug interactions with concomitant medications, this regimen may not be a safe choice for all patients (see the Panel’s statement on the drug-drug interactions for ritonavir-boosted nirmatrelvir). However, because ritonavir-boosted nirmatrelvir is the only highly effective oral antiviral available for the treatment of COVID-19, drug interactions that can be safely managed should not preclude the use of this medication.

The EPIC-HR trial excluded pregnant and lactating individuals. Ritonavir has been used extensively during pregnancy in people with HIV, which suggests that it has an acceptable safety profile during pregnancy. Based on the mechanisms of action for both nirmatrelvir and ritonavir and the available animal data, the Panel recommends ritonavir-boosted nirmatrelvir for pregnant patients because the potential benefits likely outweigh the risks.

**Sotrovimab**

Three anti-SARS-CoV-2 mAb products (bamlanivimab plus etesevimab, casirivimab plus imdevimab, and sotrovimab) have received EUAs from the FDA for the treatment of nonhospitalized patients with mild to moderate COVID-19 who are at high risk of progressing to severe disease. In the clinical trials for these agents, anti-SARS-CoV-2 mAbs reduced the risk of hospitalization or death by 70% to 85%
compared to placebo. The Omicron VOC has become the dominant variant in all regions of the United States, and it is predicted to have markedly reduced susceptibility to bamlanivimab plus etesevimab and casirivimab plus imdevimab. In vitro studies indicate that sotrovimab remains active against the Omicron VOC.

**Recommendations**

- The Panel recommends using a single intravenous (IV) infusion of **sotrovimab 500 mg** in those aged ≥12 years and weighing ≥40 kg; treatment should be administered as soon as possible and within 10 days of symptom onset (AIIa).

- Sotrovimab should be administered in a setting where severe hypersensitivity reactions, such as anaphylaxis, can be managed. Patients should be monitored during the infusion and observed for at least 1 hour after infusion.

Because the Omicron VOC has become the dominant variant in the United States and real-time testing for rare, non-Omicron variants is not routinely available, the Panel **recommends against** using **bamlanivimab plus etesevimab** or **casirivimab plus imdevimab** (AIII).

The data that support the EUA for sotrovimab come from the Phase 3 COMET-ICE trial, which included outpatients aged ≥18 years with mild to moderate COVID-19 who were at high risk for progressing to severe COVID-19 and were within 5 days of symptom onset. The primary endpoint of the study was the proportion of participants who were hospitalized for ≥24 hours or who died from any cause by Day 29. Endpoint events occurred in 3 of 291 participants (1%) in the sotrovimab arm and in 21 of 292 participants (7%) in the placebo arm ($P = 0.002$), resulting in a 6% absolute reduction and an 85% relative reduction (95% CI, 44% to 96%) in the risk of hospitalization or death among those who received sotrovimab. Although the study only enrolled participants who were within 5 days of symptom onset, the EUA allows sotrovimab to be used in people who are within 10 days of symptom onset.

**Remdesivir**

Remdesivir is currently approved by the FDA for use in hospitalized patients with COVID-19 and in nonhospitalized patients with mild to moderate COVID-19 who are at high risk of disease progression. Remdesivir has been studied in nonhospitalized patients with mild to moderate COVID-19 who were at high risk of progressing to severe disease. The PINETREE trial showed that 3 consecutive days of IV remdesivir resulted in an 87% relative reduction in the risk of hospitalization or death compared to placebo. Remdesivir is expected to be active against the Omicron VOC, although in vitro and in vivo data are currently limited. See the **Remdesivir** section for more details.

**Recommendations**

- The Panel recommends using **remdesivir 200 mg** IV on Day 1, followed by **remdesivir 100 mg** IV once daily on Days 2 and 3 in those aged ≥12 years and weighing ≥40 kg; treatment should be initiated as soon as possible and within 7 days of symptom onset (BIIa).

- Remdesivir should be administered in a setting where severe hypersensitivity reactions, such as anaphylaxis, can be managed. Patients should be monitored during the infusion and observed for at least 1 hour after infusion as clinically appropriate.

Because remdesivir requires IV infusions for 3 consecutive days, there may be logistical constraints to administering remdesivir in many settings. However, it is an option if ritonavir-boosted nirmatrelvir and sotrovimab are not available.

The Panel recommends using remdesivir, dexamethasone, or both drugs together for hospitalized patients who require supplemental oxygen (see Therapeutic Management of Hospitalized Adults With COVID-19 Treatment Guidelines)
COVID-19). When remdesivir is used in this setting, it is administered as a once-daily IV infusion for 5 days. There are rare instances when hospital resources are limited and admission to an inpatient unit is not possible for patients who need to be initiated on supplemental oxygen in the emergency department (ED) or who have increasing supplemental oxygen requirements. In this case, patients may be discharged from the ED with close monitoring and are often prescribed dexamethasone for up to 10 days. Since remdesivir is often recommended for hospitalized patients with COVID-19 who have similar oxygen needs, clinicians can consider using it in this setting. It should be noted, however, that the data on using remdesivir in this situation are limited, and administering IV infusions for up to 5 consecutive days can be difficult in the outpatient setting.

Molnupiravir
Molnupiravir is the oral prodrug of beta-D-N4-hydroxycytidine (NHC), a ribonucleoside that has broad antiviral activity against RNA viruses. NHC uptake by viral RNA-dependent RNA-polymerases results in viral mutations and lethal mutagenesis.\textsuperscript{15,16}

Molnupiravir has potent antiviral activity against SARS-CoV-2.\textsuperscript{15} As a mutagenic ribonucleoside antiviral agent, there is a theoretical risk that molnupiravir will be metabolized by the human host cell and incorporated into the host DNA, leading to mutations. Molnupiravir has been evaluated in 2 in vivo rodent mutagenicity assays. One study produced equivocal results; in the other study, there was no evidence for mutagenicity. The FDA concluded that, based on the available genotoxicity data and the 5-day duration of treatment, molnupiravir has a low risk for genotoxicity.\textsuperscript{17} In addition, there have been concerns about the potential effects of molnupiravir on SARS-CoV-2 mutation rates; the FDA is requiring the manufacturer to establish a process to monitor genomic databases for the emergence of SARS-CoV-2 variants.

Molnupiravir is expected to be active against the Omicron VOC, although in vitro and in vivo data are currently limited.\textsuperscript{9}

**Recommendation**
- The Panel recommends using molnupiravir 800 mg PO twice daily for 5 days in those aged $\geq 18$ years, but **ONLY** when ritonavir-boosted nirmatrelvir (Paxlovid), sotrovimab, and remdesivir are not available or cannot be used (CIII).

In the MOVe-OUT trial, molnupiravir reduced the rate of hospitalization or death by 30% compared to placebo in nonhospitalized patients with COVID-19.\textsuperscript{17} Even though the different treatment options have not been directly compared in clinical trials, the Panel recommends using molnupiravir only when ritonavir-boosted nirmatrelvir, sotrovimab, and remdesivir are not available or cannot be used, because molnupiravir has lower efficacy than the other options (CIII).

The FDA EUA states that molnupiravir is not recommended for use in pregnant patients due to concerns about the instances of fetal toxicity observed during animal studies. However, when other therapies are not available, pregnant people with COVID-19 who are at high risk of progressing to severe disease may reasonably choose molnupiravir therapy after being fully informed of the risks, particularly if they are beyond the time of embryogenesis (i.e., $>10$ weeks’ gestation). The prescribing clinician should document that a discussion of the risks and benefits occurred and that the patient chose this therapy.

People who engage in sexual activity that may result in conception should use effective contraception during and following treatment with molnupiravir. See the Panel’s statement on therapies for high-risk, nonhospitalized patients for more information.
**Dexamethasone**

The Panel **recommends against** the use of dexamethasone or other systemic glucocorticoids to treat outpatients with mild to moderate COVID-19 who do not require hospitalization or supplemental oxygen (AIII). There is currently a lack of safety and efficacy data on the use of these agents, and systemic glucocorticoids may cause harm in these patients. Patients who are receiving dexamethasone or another corticosteroid for other indications should continue therapy for their underlying conditions as directed by their health care providers (AIII).

In the RECOVERY trial, dexamethasone was shown to reduce mortality in hospitalized patients with COVID-19 who required supplemental oxygen. Nonhospitalized patients who did not require supplemental oxygen were not included in this trial. The Panel **recommends against** the use of dexamethasone or other systemic glucocorticoids in this population, as there are no clinical trial data to support their use (AIII).

Dexamethasone was stopped at the time of hospital discharge during the RECOVERY trial. For hospitalized patients with COVID-19 who do not require supplemental oxygen after discharge, the Panel **recommends against** the continuation of dexamethasone (AIIa).

In some cases, adult patients are deemed to be stable enough to be discharged from the inpatient setting even though they still require supplemental oxygen. This practice was likely uncommon during the RECOVERY trial; therefore, there is insufficient evidence to recommend either for or against the continued use of dexamethasone after hospital discharge in patients who require supplemental oxygen. The use of corticosteroids can lead to adverse events (e.g., hyperglycemia, neuropsychiatric symptoms, secondary infections), which may be difficult to detect and monitor in an outpatient setting. If a patient continues to receive corticosteroids after discharge, consider continuing corticosteroids for the duration of supplemental oxygen. However, the total duration of corticosteroid use **should not** exceed 10 days (including days during hospitalization). Only patients who showed good tolerance to this therapy prior to discharge should continue to receive corticosteroids after discharge, and these patients should receive oximetry monitoring and close follow-up through telehealth, visiting nurse services, or in-person visits.

In rare cases, patients with COVID-19 who require supplemental oxygen and hospital admission may need to be discharged from the ED due to scarce resources (e.g., in cases where hospital beds or staff are not available). For these patients, the Panel recommends using dexamethasone 6 mg PO once daily for the duration of supplemental oxygen (dexamethasone use should not exceed 10 days) with careful monitoring for adverse events (BIII). These patients should receive oximetry monitoring and close follow-up through telehealth, visiting nurse services, or in-person visits.

**Other Agents That Have Been Studied or Are Under Investigation for Use in Outpatients With COVID-19**

- The Panel **recommends against** the use of chloroquine or hydroxychloroquine with or without azithromycin (AI), lopinavir/ritonavir, and other HIV protease inhibitors (AIII) for the outpatient treatment of COVID-19.

- The Panel **recommends against** the use of antibacterial therapy (e.g., azithromycin, doxycycline) for the outpatient treatment of COVID-19 in the absence of another indication (AIII).

- Other agents have undergone or are currently undergoing investigation in the outpatient setting. For more information, please refer to the sections of the Guidelines that address:
  - **Antiviral agents**, such as ivermectin and nitazoxanide
• **Convalescent plasma**
• **Immunomodulators**, such as colchicine, fluvoxamine, and inhaled corticosteroids
• **Supplements**, such as vitamin C, vitamin D, and zinc

The Panel **recommends against** the use of **anticoagulants** and **antiplatelet therapy** for the prevention of venous thromboembolism or arterial thrombosis unless the patient has other indications for the therapy or is participating in a clinical trial (AIIa). For more information, see [Antithrombotic Therapy in Patients With COVID-19](https://www.covid19treatmentguidelines.nih.gov/).

Health care providers should provide information about ongoing clinical trials of investigational therapies to eligible outpatients with COVID-19 so they can make informed decisions about participation (AIII).

**Concomitant Medication Management**

In general, a patient’s usual medication and/or supplement regimen should be continued after the diagnosis of COVID-19 (see [Considerations for Using Concomitant Medications in Patients With COVID-19](https://www.covid19treatmentguidelines.nih.gov/)). **Angiotensin-converting enzyme inhibitors**, **statin therapy**, **nonsteroidal anti-inflammatory drugs**, and **oral, inhaled, and intranasal corticosteroids** that are prescribed for comorbid conditions should be continued as directed (AIII). Patients should be advised to avoid the use of nebulized medications in the presence of others to avoid potential aerosolization of SARS-CoV-2. In patients with HIV, antiretroviral therapy should not be switched or adjusted for the purpose of preventing or treating SARS-CoV-2 infection (AIII). For more information, see [Special Considerations in People With HIV](https://www.covid19treatmentguidelines.nih.gov/).

When a patient is receiving an immunomodulating medication, the prescribing clinician should be consulted about the risks and benefits that are associated with a temporary dose reduction or discontinuation; these risks and benefits will depend on the medication’s indication and the severity of the underlying condition.

Patients who use a continuous positive airway pressure (CPAP) device or a bilevel positive airway pressure (BiPAP) device to manage obstructive sleep apnea may continue to use their machine. As with nebulizers, patients should be advised to use the device only when they are isolated from others.

**References**


Figure 2. Therapeutic Management of Hospitalized Adults With COVID-19 Based on Disease Severity

Dosing regimens for the drugs recommended in this figure are listed in Table A below.

<table>
<thead>
<tr>
<th>DISEASE SEVERITY</th>
<th>PANEL’S RECOMMENDATIONS</th>
</tr>
</thead>
</table>
| Hospitalized but Does Not Require Supplemental Oxygen | The Panel recommends against the use of dexamethasone (Allo) or other corticosteroids (Alli).<sup>a</sup>  
There is insufficient evidence to recommend either for or against the routine use of remdesivir. For patients at high risk of disease progression, remdesivir may be appropriate. |
| Hospitalized and Requires Supplemental Oxygen         | Use 1 of the following options:  
  - Remdesivir<sup>b,c</sup> (e.g., for patients who require minimal supplemental oxygen) (Blia)  
  - Dexamethasone plus remdesivir<sup>b,c</sup> (Blib)  
  - Dexamethasone (Bl)  
For patients on dexamethasone with rapidly increasing oxygen needs and systemic inflammation, add a second immunomodulatory drug<sup>d</sup> (e.g., baricitinib<sup>e</sup> or tocilizumab<sup>f</sup>) (Cllia). |
| Hospitalized and Requires Oxygen Through a High-Flow Device or NIV | Use 1 of the following options:  
  - Dexamethasone (Al)  
  - Dexamethasone plus remdesivir<sup>g</sup> (Blil)  
For patients with rapidly increasing oxygen needs and systemic inflammation, add either baricitinib<sup>h</sup> (Blia) or IV tocilizumab<sup>i</sup> (Blia) to 1 of the 2 options above.<sup>[f,g,l]</sup> |
| Hospitalized and Requires MV or ECMO                  | • Dexamethasone (Al)<sup>j</sup>  
For patients who are within 24 hours of admission to the ICU:  
  - Dexamethasone plus IV tocilizumab (Blia)  
If IV tocilizumab is not available or not feasible to use, IV sarilumab can be used (Blia). |

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

<sup>a</sup> Corticosteroids prescribed for an underlying condition should be continued.
<sup>b</sup> If the patient progresses to requiring high-flow oxygen, NIV, MV, or ECMO, complete the full course of remdesivir (refer to Table A).
<sup>c</sup> Evidence suggests that the benefit of remdesivir is greatest when the drug is given early in the course of COVID-19 (e.g., within 10 days of symptom onset). Clinical trials have not demonstrated a mortality benefit for remdesivir, but a large placebo-controlled trial showed that remdesivir reduced time to clinical recovery in hospitalized patients. See Rationale for the Use of Remdesivir below.
<sup>d</sup> Drugs are listed alphabetically. There are no studies directly comparing baricitinib and tocilizumab, and there is insufficient evidence to recommend 1 drug or 1 class of drug (i.e., JAK inhibitors, anti-IL-6 receptor mAbs) over the other. Treatment decisions should be based on local guidance, drug availability, and patient comorbidities.
<sup>e</sup> If baricitinib and IV tocilizumab are not available or not feasible to use, tofacitinib can be used instead of baricitinib (Blia) and IV sarilumab can be used instead of IV tocilizumab (Blia).
<sup>f</sup> The Panel recommends against the use of baricitinib in combination with tocilizumab for the treatment of COVID-19, except in a clinical trial (Alia). Because both baricitinib and tocilizumab are potent immunosuppressants, there is the potential for an additive risk of infection.
<sup>g</sup> The combination of dexamethasone plus remdesivir may be considered for patients who have recently been intubated (CIII). The Panel recommends against the use of remdesivir monotherapy in these patients (Alla).

Key: ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; IL = interleukin; IV = intravenous; JAK = Janus kinase; mAb = monoclonal antibody; MV = mechanical ventilation; NIV = noninvasive ventilation; the Panel = the COVID-19 Treatment Guidelines Panel; PO = orally
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remdesivir</td>
<td>RDV 200 mg IV once, then RDV 100 mg IV once daily for 4 days or until hospital discharge.</td>
<td>• If the patient progresses to more severe illness, complete the course of RDV. • For a discussion on using RDV in patients with renal insufficiency, see Remdesivir.</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>DEX 6 mg IV or PO once daily for up to 10 days or until hospital discharge.</td>
<td>• If DEX is not available, an equivalent dose of another corticosteroid may be used. • For more information, see Corticosteroids.</td>
</tr>
<tr>
<td>Baricitinib</td>
<td>Baricitinib dose is dependent on eGFR; duration of therapy is up to 14 days or until hospital discharge.</td>
<td>• eGFR ≥60 mL/min/1.73 m²: Baricitinib 4 mg PO once daily • eGFR 30 to &lt;60 mL/min/1.73 m²: Baricitinib 2 mg PO once daily • eGFR 15 to &lt;30 mL/min/1.73 m²: Baricitinib 1 mg PO once daily • eGFR &lt;15 mL/min/1.73 m²: Baricitinib is not recommended.</td>
</tr>
<tr>
<td>Tofacitinib</td>
<td>Tofacitinib 10 mg PO twice daily for up to 14 days or until hospital discharge.</td>
<td>• Use as an alternative immunomodulatory drug if baricitinib is not available or not feasible to use (BIIa). • eGFR &lt;60 mL/min/1.73 m²: Tofacitinib 5 mg PO twice daily</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>Tocilizumab 8 mg/kg actual body weight (up to 800 mg) administered as a single IV dose.</td>
<td>• In clinical trials, a third of the participants received a second dose of tocilizumab 8 hours after the first dose if no clinical improvement was observed.</td>
</tr>
<tr>
<td>Sarilumab</td>
<td>Use the single-dose, prefilled syringe (not the prefilled pen) for SQ injection. Reconstitute sarilumab 400 mg in 100 cc 0.9% NaCl and administer as an IV infusion over 1 hour.</td>
<td>• Use as an alternative immunomodulatory drug if tocilizumab is not available or not feasible to use (BIIa). • In the United States, the currently approved route of administration for sarilumab is SQ injection. In the REMAP-CAP trial, the SQ formulation was used to prepare the IV infusion.</td>
</tr>
</tbody>
</table>

**Key:** DEX = dexamethasone; eGFR = estimated glomerular filtration rate; IV = intravenous; PO = oral; RDV = remdesivir; SQ = subcutaneous

**Introduction**

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. Subsequently, the disease appears to be also driven by a dysregulated immune/inflammatory response to SARS-CoV-2 that leads to tissue damage. Based on this understanding, therapies that directly target SARS-CoV-2 are anticipated to have the greatest effect early in the course of the disease, whereas immunosuppressive/anti-inflammatory therapies are likely to be more beneficial after COVID-19 has progressed to stages characterized by hypoxia.

**Patients Who Do Not Require Supplemental Oxygen**

**Recommendations**

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends against the use of dexamethasone (AIIa) or other corticosteroids (AIII) for the treatment of COVID-19. Patients with COVID-19 who are receiving dexamethasone or another corticosteroid for an underlying condition should continue this therapy as directed by their health care provider.
- There is insufficient evidence to recommend either for or against the routine use of remdesivir for the treatment of COVID-19 in hospitalized patients who do not require supplemental oxygen, but use may be appropriate in patients at high risk of disease progression.
Rationale for Recommending Against the Use of Dexamethasone or Other Corticosteroids

In the RECOVERY trial, a multicenter, open-label trial in the United Kingdom, hospitalized patients with COVID-19 were randomized to receive dexamethasone plus standard of care or standard of care alone (control arm).\(^1\) No survival benefit for dexamethasone was observed among the participants who did not require supplemental oxygen at enrollment: 17.8% of participants in the dexamethasone arm and 14% in the control arm died within 28 days of enrollment (rate ratio 1.19; 95% CI, 0.91–1.55). See Table 4a for additional information. Based on these data, the Panel recommends against the use of dexamethasone (AIIa) or other corticosteroids (AIII) for the treatment of COVID-19 in hospitalized patients who do not require supplemental oxygen, unless the patient has another indication for corticosteroid therapy.

Rationale for Determining That There Is Insufficient Evidence to Recommend Either for or Against the Use of Remdesivir

ACTT-1 was a multinational randomized controlled trial that compared intravenous (IV) remdesivir to placebo in hospitalized patients with COVID-19. Remdesivir showed no significant benefit in patients with mild to moderate disease, which was defined as oxygen saturation >94% on room air or a respiratory rate <24 breaths/min without supplemental oxygen (rate ratio for recovery 1.29; 95% CI, 0.91–1.83); however, there were only 138 patients in this subgroup.\(^2\)

In a manufacturer-sponsored, open-label randomized trial that included 596 patients with moderate COVID-19, patients who received 5 days of remdesivir had higher odds of a better clinical status on Day 11 (based on a 7-point ordinal scale) than those who received standard of care (OR 1.65; 95% CI, 1.09–2.48; \(P = 0.02\)).\(^3\)

The Solidarity trial was a large, multinational, open-label randomized controlled trial that compared a 10-day course of remdesivir to standard of care. About 25% of hospitalized patients in both arms did not require supplemental oxygen at study entry. The primary outcome of in-hospital mortality occurred in 11 of 661 patients (2%) in the remdesivir arm and 13 of 664 patients (2.1%) in the control arm (rate ratio 0.90; 99% CI, 0.31–2.58).\(^4\) Please see Table 2a for additional information.

Data supporting the clinical benefit of early treatment with remdesivir emerged from PINETREE, a randomized placebo-controlled trial in nonhospitalized patients with COVID-19 at high risk of clinical progression. Participants were randomized to receive 3 days of IV remdesivir or placebo as outpatients. At treatment initiation, the median duration of symptoms was 5 days. By Day 28, there was a significant decrease in hospitalization and/or death among the patients who received remdesivir: the primary endpoint occurred in 0.7% of remdesivir recipients versus 5.3% of placebo recipients (HR 0.13; 95% CI, 0.03–0.59; \(P = 0.008\)).\(^5\)

Because these trials produced conflicting results regarding the benefits of remdesivir, the Panel finds the available evidence insufficient to recommend either for or against routine treatment with remdesivir for all hospitalized patients with moderate COVID-19. However, the Panel recognizes that clinicians may judge that remdesivir is appropriate for some hospitalized patients with moderate disease (e.g., those at particularly high risk for clinical deterioration).

Patients Who Require Supplemental Oxygen

Patients who require supplemental oxygen, but not high-flow oxygen, noninvasive ventilation (NIV), or mechanical ventilation are a heterogeneous group. Some of these patients will have mild disease that will improve after a short period with or without treatment with remdesivir, dexamethasone, or both; others will develop progressive disease despite treatment and require a more intensive level of care. There is no consensus on which clinical or laboratory parameters allow for reliable risk-stratification to guide therapy and/or identify which subsets of patients will experience progressive lung injury and hypoxemia.
Some studies have tried to define this group according to traditional risk factors for COVID-19 progression and/or by the presence of elevated inflammatory markers like C-reactive protein (CRP), but evidence to support a specific identifying biomarker or clinical threshold is lacking.

**Recommendations**

The Panel recommends using 1 of the following options for hospitalized patients who require supplemental oxygen:

- **Remdesivir** (e.g., for patients who require minimal supplemental oxygen) (BIIa)
- **Dexamethasone plus remdesivir** (BIIb)
- **Dexamethasone** (BI); for patients on dexamethasone who have rapidly increasing oxygen needs and systemic inflammation, add a second immunomodulatory drug (e.g., tocilizumab or baricitinib) (CIIa)

If dexamethasone is not available, an alternative corticosteroid such as prednisone, methylprednisolone, or hydrocortisone can be used (BIII). See [Corticosteroids](https://www.covid19treatmentguidelines.nih.gov/) for dosing recommendations.

**Rationale for the Use of Remdesivir**

In the ACTT-1 trial, remdesivir was associated with improved time to recovery in the 435 participants who required oxygen supplementation but not high-flow oxygen, NIV, or mechanical ventilation (7 days for remdesivir vs. 9 days for placebo; recovery rate ratio 1.45; 95% CI, 1.18–1.79). Fewer patients in the remdesivir arm than in the placebo arm progressed to requiring high-flow oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) (17% vs. 24%). In a post hoc analysis of deaths by Day 29, remdesivir appeared to confer a substantial survival benefit in this subgroup (HR for death 0.30; 95% CI, 0.14–0.64).

The Solidarity trial reported no difference in the rate of in-hospital deaths between patients who received remdesivir and those who received standard of care (rate ratio for death in the overall study population 0.95; 95% CI, 0.81–1.11; rate ratio for death in patients who did not require mechanical ventilation at entry 0.86; 99% CI, 0.67–1.11). There was no difference between patients who received remdesivir and those who received standard of care in the percentage of those who progressed to mechanical ventilation (11.9% vs. 11.5%) or in length of hospital stay. However, an open-label trial like Solidarity is less well-suited to assess time to recovery than a placebo-controlled trial. In the Solidarity trial, because both clinicians and patients knew that remdesivir was being administered, it is possible that hospital discharge was delayed in order to complete the 10-day course of therapy.

DisCoVeRy was a multinational, open-label randomized controlled trial that compared up to 10 days of remdesivir plus standard of care to standard of care alone in hospitalized patients with moderate or severe COVID-19. There was no significant difference in the odds of improved clinical status by Day 15 between the patients in the remdesivir arm and the standard of care arm (OR 0.98; 95% CI, 0.77–1.25). At Day 28, there were also no differences between the arms in either mortality (8% in remdesivir arm vs. 9% in standard of care arm) or clinical status. The DisCoVeRy trial shared with the Solidarity trial the major limitation of open-label design. Additionally, 440 of the 832 participants in the DisCoVeRy trial (219 in the remdesivir arm and 221 in the standard of care arm) were also Solidarity trial participants.

Although the open-label Solidarity and DisCoVeRy trials demonstrated no mortality benefit for remdesivir, in the large randomized placebo-controlled ACTT-1 trial, remdesivir significantly reduced time to clinical recovery. In a post hoc analysis, this clinical benefit of remdesivir was most evident in those who had symptoms for ≤10 days. The evidence from the ACTT-1 and PINETREE trials suggests that remdesivir will have its greatest impact when administered early in the clinical course, which is...
also the case for antiviral agents used to treat other viral infections. The Panel recommends remdesivir (without dexamethasone) as a treatment option for certain patients with COVID-19 who require minimal supplemental oxygen and are in the early course of the disease (BIIa). In these individuals, the hyperinflammatory state where corticosteroids might be most beneficial may not yet be present or fully developed.

Although several trials studied a 10-day course of remdesivir, a 5-day course has been shown to be comparable to 10 days of therapy in hospitalized patients with moderate-to-severe COVID-19. For more information, please see Table 2a.

Rationale for the Use of Remdesivir Plus Dexamethasone

Data on the safety and efficacy of combination therapy consisting of remdesivir with corticosteroids are primarily derived from observational studies, with some (but not all) suggesting a clinical benefit of remdesivir plus dexamethasone. Remdesivir plus dexamethasone has not been directly compared to dexamethasone alone in a large randomized clinical trial. Patients with severe COVID-19 may develop a systemic inflammatory response that leads to multiple organ dysfunction syndrome. The potent anti-inflammatory effects of corticosteroids might prevent or mitigate these hyperinflammatory effects. Thus, the combination of an antiviral agent, such as remdesivir, with an anti-inflammatory agent, such as dexamethasone, may treat the viral infection and dampen the potentially injurious inflammatory response that is a consequence of the infection.

Based on the theoretical combined benefit of antiviral and anti-inflammatory therapies, the Panel recommends the combination of dexamethasone plus remdesivir as a treatment option for patients who require supplemental oxygen (BIIb), despite important limitations of observational data.

Rationale for the Use of Dexamethasone

In the RECOVERY trial, treatment with dexamethasone conferred a survival benefit among participants who required supplemental oxygen at enrollment. Among these participants, fewer participants in the dexamethasone arm than in the standard of care arm died within 28 days of enrollment (23.3% vs. 26.2%; rate ratio 0.82; 95% CI, 0.72–0.94). However, the amount of supplemental oxygen that participants were receiving and the proportions of participants who required oxygen through a high-flow device or NIV were not reported. It is possible that the benefit of dexamethasone was greatest in those who required more respiratory support. It should be noted that <0.1% of patients in the RECOVERY trial received concomitant remdesivir. For more information, see Corticosteroids.

Some experts prefer not to use dexamethasone monotherapy in patients who require supplemental oxygen because of the theoretical concern that corticosteroids might slow viral clearance when administered without an antiviral drug. Corticosteroids have been associated with delayed viral clearance and/or worse clinical outcomes in patients with other viral respiratory infections. Some studies have suggested that corticosteroids slow SARS-CoV-2 clearance, but the results to date are inconclusive.

Rationale for Adding a Second Immunomodulatory Drug to Dexamethasone in Certain Patients Who Require Rapidly Increasing Oxygen Supplementation

Several major randomized trials evaluating the use of interleukin (IL)-6 inhibitors or Janus Kinase (JAK) inhibitors with or without corticosteroids in patients with COVID-19 have included patients who required only low-flow supplemental oxygen. However, subgroup analyses in these trials have not clearly defined which patients in this heterogeneous group are most likely to benefit from corticosteroids with another immunomodulator. Direct comparison between trials is not possible because in some trials, background therapies (e.g., corticosteroids) and inclusion criteria (e.g., the requirement for elevated inflammatory markers) differed. Nonetheless, some trials suggest that adding a second immunomodulator to
dexamethasone provided benefits in patients requiring low-flow supplemental oxygen.\textsuperscript{19-21} For example, the RECOVERY trial demonstrated a mortality benefit for adding tocilizumab to dexamethasone compared to usual care alone (including dexamethasone) in a subgroup that included patients on low-flow oxygen.\textsuperscript{19} Similarly, data on JAK inhibitors are also inconclusive; for example, the COV-BARRIER trial did not find a statistically significant benefit of baricitinib versus placebo in patients on low-flow oxygen,\textsuperscript{20} whereas the placebo-controlled STOP-COVID trial demonstrated a reduction in respiratory failure or death in the subgroup of patients on low-flow oxygen who received tofacitinib.\textsuperscript{21}

Given the uncertainty concerning which patients in this group would benefit from adding a second immunomodulator, such as baricitinib or tocilizumab, to dexamethasone treatment, the Panel recommends considering these therapies on a case-by-case basis for individuals with rapidly increasing oxygen requirements and elevated markers of systemic inflammation (CIIa). Because there are no studies that directly compare the use of baricitinib and tocilizumab as treatments for COVID-19, the Panel has insufficient evidence to recommend 1 drug over the other. Treatment decisions should be based on local guidance, drug availability, and patient comorbidities.

### Additional Considerations

- Baricitinib or tocilizumab should only be given in combination with dexamethasone or another corticosteroid. Some clinicians may assess a patient’s clinical response to dexamethasone before deciding whether adding baricitinib or tocilizumab as a second immunomodulatory drug is necessary.
- Because there are no studies that directly compare the use of baricitinib and tocilizumab as treatments for COVID-19, the Panel has insufficient evidence to recommend 1 drug or class of drugs (i.e., JAK inhibitors, anti-IL-6 receptor mAbs) over the other. Treatment decisions should be based on local guidance, drug availability, and patient comorbidities.
- If baricitinib and IV tocilizumab are not available or not feasible to use, tofacitinib can be used instead of baricitinib (BIIa) and IV sarilumab can be used instead of IV tocilizumab (BIIa).
- The Panel recommends against the use of baricitinib in combination with tocilizumab for the treatment of COVID-19, except in a clinical trial (AIII). Because both baricitinib and tocilizumab are potent immunosuppressants, there is the potential for an additive risk of infection.
- Combination immunosuppressive therapy (e.g., dexamethasone with baricitinib or tocilizumab) may increase the risk of opportunistic infections or reactivation of latent infections; however, randomized trials to date have not demonstrated an increase in the frequency of infections.
- Cases of severe and disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with tocilizumab and corticosteroids.\textsuperscript{22,23} Many clinicians would initiate empiric treatment for strongyloidiasis (e.g., with the antiparasitic drug ivermectin) with or without serologic testing in patients from areas where \textit{Strongyloides} is endemic (i.e., tropical, subtropical, or warm temperate areas).

### Patients Who Require Oxygen Through a High-Flow Device or Noninvasive Ventilation

**Recommendations**

- The Panel recommends using 1 of the following options for hospitalized patients who require oxygen through a high-flow device or NIV:
  - Dexamethasone (AI)
  - Dexamethasone plus remdesivir (BIII)
- For patients who have rapidly increasing oxygen needs and have increased markers of
inflammation, add either baricitinib (BIIa) or tocilizumab (BIIa) (drugs are listed alphabetically) to 1 of the 2 options above.

**Additional Considerations**

- If dexamethasone is not available, an equivalent dose of another corticosteroid such as prednisone, methylprednisolone, or hydrocortisone may be used (BIII). See Corticosteroids for more information.
- Immunosuppressive therapy (e.g., dexamethasone with or without baricitinib or tocilizumab) may increase the risk of opportunistic infections or reactivation of latent infections; however, randomized trials to date have not demonstrated an increase in the frequency of infections.
- Cases of severe and disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with tocilizumab and corticosteroids. Many clinicians would initiate empiric treatment for strongyloidiasis (e.g., with the antiparasitic drug ivermectin) with or without serologic testing in patients from areas where *Strongyloides* is endemic (i.e., tropical, subtropical, or warm temperate areas).

**Rationale for the Use of Dexamethasone**

In the RECOVERY trial, treatment with dexamethasone conferred a survival benefit among participants who required supplemental oxygen without mechanical ventilation at enrollment: 23.3% of the participants in the dexamethasone arm versus 26.2% in the standard of care arm died within 28 days of enrollment (rate ratio 0.82; 95% CI, 0.72–0.94).

**Rationale for the Use of Remdesivir Plus Dexamethasone**

As discussed above, data on the safety and efficacy of combination therapy of remdesivir with corticosteroids are primarily derived from observational studies, with some, but not all suggesting clinical benefit of remdesivir plus dexamethasone. Remdesivir plus dexamethasone has not been directly compared to dexamethasone alone in a large randomized clinical trial. Patients with severe COVID-19 may develop a systemic inflammatory response that leads to multiple organ dysfunction syndrome. The potent anti-inflammatory effects of corticosteroids might prevent or mitigate these hyperinflammatory effects. Thus, the combination of an antiviral agent, such as remdesivir, with an anti-inflammatory agent, such as dexamethasone, may treat the viral infection and dampen the potentially injurious inflammatory response that is a consequence of the infection. Based on the theoretical combined benefit of antiviral and anti-inflammatory therapies, the Panel recommends the combination of dexamethasone plus remdesivir as a treatment option for patients who require high-flow oxygen or NIV (BIIb), despite important limitations of observational data.

**Rationale for Not Recommending Remdesivir Monotherapy**

In the ACTT-1 trial, there was no observed difference in time to recovery between the remdesivir and placebo arms in the subgroup of 193 participants who required high-flow oxygen or NIV at enrollment (recovery rate ratio 1.09; 95% CI, 0.76–1.57). A post hoc analysis did not show a survival benefit for remdesivir at Day 29, but the trial was not powered to detect this difference. The Panel does not recommend using remdesivir monotherapy in patients who require high-flow oxygen or NIV because there is uncertainty regarding whether remdesivir alone confers a clinical benefit in this subgroup (AIIa). Dexamethasone alone or remdesivir plus dexamethasone are better treatment options for COVID-19 in this group of patients.

For patients who start remdesivir monotherapy and then progress to requiring oxygen through a high-flow device or NIV, the Panel recommends initiating dexamethasone and continuing remdesivir...
until the treatment course is completed. Clinical trials that evaluated the use of remdesivir categorized patients based on their severity of illness at the start of treatment with remdesivir; therefore, patients may benefit from remdesivir even if their clinical course progresses to a severity of illness for which the benefits of remdesivir are less certain.

**Rationale for Adding a Second Immunomodulatory Drug to Dexamethasone in Certain Hospitalized Patients**

Several large clinical trials suggest that adding a second immunomodulatory drug, such as baricitinib or tocilizumab, to dexamethasone provides clinical benefit in patients who require oxygen supplementation through a high-flow device or NIV.

The REMAP-CAP and RECOVERY trials, the 2 largest randomized controlled trials of tocilizumab to date, have both reported a mortality benefit for tocilizumab among patients with rapid respiratory decompensation who require oxygen delivery through a high-flow device or NIV.\(^{19,24}\) Most patients in both studies received corticosteroids.

In the REMAP-CAP trial, patients admitted to an intensive care unit (ICU) with severe-to-critical COVID-19 and rapid respiratory decompensation were randomized to receive open-label tocilizumab or usual care. The use of tocilizumab reduced in-hospital mortality (28% in tocilizumab arm vs. 36% in usual care arm) and, during 21 days of follow-up, increased the median number of days free of respiratory and cardiovascular organ support (10 days in tocilizumab arm vs. 0 days in usual care arm; OR 1.64; 95% CI, 1.25–2.14). Enrollment occurred within 24 hours of ICU admission and within a median of 1.2 days of hospitalization (IQR 0.8–2.8 days), suggesting that the benefit of tocilizumab occurs in patients experiencing rapid respiratory decompensation. The RECOVERY trial also suggested a mortality benefit for tocilizumab plus dexamethasone in a subset of patients that included those who required NIV or high-flow oxygen. In this study, a subset of participants with hypoxemia and CRP ≥75 mg/L were randomized to receive tocilizumab or usual care. Tocilizumab reduced all-cause mortality in these patients; by Day 28, 29% of participants in the tocilizumab arm versus 33% in the usual care arm had died (rate ratio 0.86; 95% CI, 0.77–0.96).

In the COV-BARRIER trial, 1,525 hospitalized patients with COVID-19 and ≥1 elevated inflammatory biomarker were randomized 1:1 to receive oral baricitinib 4 mg or placebo in addition to the local standard of care for up to 14 days (or until hospital discharge).\(^{20}\) Overall, there was no difference in the occurrence of the primary endpoint of progression to high-flow oxygen, NIV, mechanical ventilation, or death by Day 28 between the baricitinib arm (27.8% of patients) and the placebo arm (30.5% of patients; OR 0.85; 95% CI, 0.67–1.08; \(P = 0.18\)). However, all-cause mortality by Day 28 was 8.1% in the baricitinib arm and 13.1% in the placebo arm, resulting in a 38.2% reduction in mortality for baricitinib (HR 0.57; 95% CI, 0.41–0.78; nominal \(P = 0.002\)). The difference in mortality was most pronounced in the subgroup of 370 patients receiving high-flow oxygen or NIV at baseline (17.5% in the baricitinib arm vs. 29.4% in the placebo arm; HR 0.52; 95% CI, 0.33–0.80; nominal \(P = 0.007\)). The occurrence of adverse events, serious adverse events, serious infections, and venous thromboembolic events in the arms was comparable.

The ACTT-2 trial demonstrated that baricitinib used in combination with remdesivir improved time to recovery in hospitalized patients with COVID-19. The effect was most pronounced in patients who were receiving high-flow oxygen or NIV. However, patients receiving corticosteroids were excluded from the ACTT-2 trial, limiting the generalizability of these findings.

Given the clinical trial data (see Table 4e), the Panel recommends adding baricitinib or tocilizumab as a second immunomodulatory treatment in combination with dexamethasone for patients who are receiving oxygen supplementation through a high-flow device or NIV (BIIa).
**Additional Considerations**

- Baricitinib or tocilizumab should only be given in combination with dexamethasone or another corticosteroid. Some clinicians may assess a patient’s clinical response to dexamethasone before deciding whether adding baricitinib or tocilizumab is necessary.

- Studies that directly compare baricitinib to tocilizumab as treatments for COVID-19 are not available. Therefore, there is insufficient evidence for the Panel to recommend 1 drug over the other. Treatment decisions should be based on local guidance, drug availability, and patient comorbidities.

- If baricitinib and IV tocilizumab are not available or not feasible to use, tofacitinib can be used instead of baricitinib (BIIa) and IV sarilumab can be used instead of IV tocilizumab (BIIa).

- Although approximately a third of patients in the REMAP-CAP and RECOVERY trials received a second dose of tocilizumab at the discretion of their treating physician, data on outcomes based on receipt of 1 or 2 doses is not available. Therefore, there is insufficient evidence to determine which patients, if any, would benefit from an additional dose of the drug.

**Rationale for Recommending Against the Use of the Combination of Baricitinib and Tocilizumab**

The Panel recommends against the use of the combination of baricitinib and tocilizumab for the treatment of COVID-19, except in a clinical trial (AIII), because there is insufficient evidence for the use of this combination. Given that both baricitinib and tocilizumab are potent immunosuppressants, there is the potential for an additive risk of infection.

**Rationale for Recommending Sarilumab and Dexamethasone as an Alternative to Tocilizumab and Dexamethasone in Certain Hospitalized Patients**

In an updated report from the REMAP-CAP trial, the efficacy of tocilizumab and sarilumab in improving survival and reducing the duration of organ support was similar. Compared to noncontemporary control patients who received placebo plus dexamethasone, patients who received sarilumab and dexamethasone demonstrated reduced mortality, shorter time to ICU discharge, and more organ support-free days.

In the REMAP-CAP trial, sarilumab in combination with dexamethasone (n = 483) was noninferior to tocilizumab with dexamethasone (n = 943) with regards to the number of organ support-free days and mortality with a probability of 99% and 98%, respectively.

Even though the REMAP-CAP trial supports that sarilumab and tocilizumab have similar efficacy in the treatment of hospitalized patients with COVID-19, the Panel recommends sarilumab only when tocilizumab is not available or is not feasible to use (BIIa). The rationales for this recommendation are:

- The evidence of efficacy for tocilizumab is more extensive than for sarilumab, and
- Currently, sarilumab is only approved as a subcutaneous (SQ) injection in the United States.

In the REMAP-CAP trial, a single dose of sarilumab 400 mg for SQ injection was reconstituted in 50 ml or 100 ml of normal saline and administered as an IV infusion over 1 hour.

**Rationale for Recommending the Use of Tofacitinib Plus Dexamethasone in Certain Hospitalized Patients**

In the STOP-COVID trial, a double-blind randomized placebo-controlled trial, use of tofacitinib was associated with a decreased risk of respiratory failure and death (risk ratio 0.63; 95% CI, 0.41–0.97).
All-cause mortality within 28 days was 2.8% in the tofacitinib arm (n = 144) and 5.5% in the placebo arm (n = 145) (HR 0.49; 95% CI, 0.15–1.63). Approximately 80% of participants in each arm also received corticosteroids.21

The STOP-COVID trial supports that tofacitinib plus steroids is effective in improving outcomes in hospitalized patients with COVID-19. Both baricitinib and tofacitinib belong to the same class of anti-inflammatory drugs, the kinase inhibitors, and have overlapping mechanisms of action. The Panel recommends tofacitinib as an alternative to baricitinib only when baricitinib is not available or not feasible to use (BIIa) because the evidence of efficacy for tofacitinib is less extensive than for baricitinib.

Patients Who Require Mechanical Ventilation or Extracorporeal Membrane Oxygenation

Recommendations

- The Panel recommends using dexamethasone for hospitalized patients with COVID-19 who require mechanical ventilation or ECMO (AI).
- The Panel recommends using dexamethasone plus tocilizumab for patients with COVID-19 who are within 24 hours of admission to the ICU (BIIa).

Additional Considerations

- If dexamethasone is not available, an equivalent dose of an alternative corticosteroid (e.g., prednisone, methylprednisolone, hydrocortisone) may be used (BIII).
- For patients who initially received remdesivir monotherapy and progressed to requiring mechanical ventilation or ECMO, dexamethasone should be initiated and remdesivir should be continued until the treatment course is completed.
- The Panel recommends against the initiation of remdesivir monotherapy (AIIa) in patients who require mechanical ventilation or ECMO.
- Tocilizumab should be given only in combination with dexamethasone (or another corticosteroid at an equivalent dose).
- Although some patients in the REMAP-CAP and RECOVERY trials received a second dose of tocilizumab at the discretion of their treating physician, there is insufficient evidence to determine which patients, if any, would benefit from an additional dose of the drug.
- The combination of dexamethasone and tocilizumab may increase the risk of opportunistic infections or reactivation of latent infections. Prophylactic treatment for strongyloidiasis (e.g., with the antiparasitic drug ivermectin) should be considered for patients who are from areas where Strongyloides is endemic.

Rationale for the Use of Dexamethasone Monotherapy

As COVID-19 progresses, a systemic inflammatory response may lead to multiple organ dysfunction syndrome. The anti-inflammatory effects of corticosteroids mitigate the inflammatory response, and the use of corticosteroids has been associated with improved outcomes in people with critical COVID-19.

Dexamethasone reduces mortality in critically ill patients with COVID-19 according to a meta-analysis that aggregated 7 randomized trials and included data on 1,703 critically ill patients.26 The largest trial in the meta-analysis was the RECOVERY trial, whose subgroup of mechanically ventilated patients was included.1 For details about the meta-analysis and the RECOVERY trial, see Corticosteroids and Table 4a. Because the benefits of dexamethasone outweigh the potential harms, the Panel recommends using dexamethasone in hospitalized patients with COVID-19 who require mechanical ventilation or ECMO (AI).
**Considerations Related to the Use of Dexamethasone Plus Remdesivir Combination Therapy**

Dexamethasone plus remdesivir combination therapy has not been evaluated in controlled studies; therefore, there is insufficient information to make a recommendation either for or against the use of this combination therapy. However, there is a theoretical reason to administer dexamethasone plus remdesivir to patients who have recently been intubated. Antiviral therapy may prevent a steroid-related delay in viral clearance. This delay has been reported in the setting of other viral infections.\(^{11,12}\)

Some studies have suggested that corticosteroids slow SARS-CoV-2 clearance, but the studies to date are not definitive. For example, an observational study in patients with nonsevere COVID-19 suggested that viral clearance was delayed in those who received corticosteroids,\(^{27}\) whereas a more recent study in patients with moderate to severe COVID-19 found no relationship between the use of corticosteroids and the rate of viral clearance.\(^{18}\) Given the conflicting results from observational studies and the lack of clinical trial data, some Panel members would coadminister dexamethasone and remdesivir in patients who have recently been placed on mechanical ventilation (CIII) until more conclusive evidence becomes available, based on their concerns about delayed viral clearance in patients who received corticosteroids. Other Panel members would not coadminister dexamethasone and remdesivir due to uncertainties about the benefit of using remdesivir in critically ill patients.

**Rationale for Recommending the Use of Tocilizumab Plus Dexamethasone in Patients Within 24 Hours of Admission to the Intensive Care Unit**

The REMAP-CAP and RECOVERY trials, the 2 largest randomized controlled trials of tocilizumab to date, both reported a mortality benefit for tocilizumab in patients who experienced rapid respiratory decompensation and were recently admitted to the ICU, including those who required mechanical ventilation.\(^{19,24}\) The REMAP-CAP trial enrolled patients within 24 hours of admission to the ICU. Previous trials that enrolled patients later in the course of ICU care and/or who received oxygen support >24 hours after ICU admission have failed to show consistent clinical benefits for tocilizumab (see Table 4e). Thus, it is unclear whether there is a clinical benefit for tocilizumab in patients who received mechanical ventilation for >24 hours. Findings from the RECOVERY trial suggest a clinical benefit for tocilizumab plus corticosteroids among patients with rapid clinical progression who received mechanical ventilation. Please see the Rationale for Adding a Second Immunomodulatory Drug to Dexamethasone in Certain Hospitalized Patients section above for additional details on the clinical trial data and rationale for using tocilizumab in this situation.

**Rationale for Recommending Against the Use of Remdesivir Monotherapy**

A clear benefit of remdesivir monotherapy has not been demonstrated in patients who require mechanical ventilation or ECMO. In the ACTT-1 trial, remdesivir did not improve the recovery rate in this subgroup of participants (recovery rate ratio 0.98; 95% CI, 0.70–1.36), and in a post hoc analysis of deaths by Day 29, remdesivir did not improve survival in this subgroup (HR 1.13; 95% CI, 0.67–1.89).\(^2\) In the Solidarity trial, there was a trend toward increased mortality among patients who received mechanical ventilation and were randomized to receive remdesivir rather than standard of care (rate ratio 1.27; 95% CI, 0.99–1.62).\(^4\) Taken together, these results do not demonstrate a clear benefit of remdesivir in critically ill patients.

For patients who start remdesivir monotherapy and then progress to requiring mechanical ventilation or ECMO, the Panel recommends initiating dexamethasone and continuing remdesivir until the treatment course is completed. Clinical trials that evaluated remdesivir categorized patients based on their severity of illness at study enrollment; therefore, patients may benefit from receiving remdesivir even if their clinical course progresses to a severity of illness for which the benefits of remdesivir are less certain.
Rationale for Recommending the Use of Sarilumab and Dexamethasone as an Alternative to Tocilizumab and Dexamethasone in Certain Hospitalized Patients

Please refer to the Patients Who Require Oxygen Through a High-Flow Device or Noninvasive Ventilation section above for the rationale regarding the use of sarilumab and dexamethasone as an alternative to tocilizumab and dexamethasone in certain hospitalized patients.

Rationale for Determining That There is Insufficient Evidence to Recommend the Use of Baricitinib in Addition to Standard of Care in Mechanically Ventilated Individuals

A cohort of critically ill patients was added to the COV-BARRIER trial after the completion of the original study. The results for the cohort were not included in the primary results of the main trial. In this addendum, 101 patients on mechanical ventilation or ECMO were randomized 1:1 to receive baricitinib 4 mg (n = 51) or placebo (n = 50) for up to 14 days in combination with standard of care. Baricitinib significantly reduced 28-day all-cause mortality (39.2% in the baricitinib arm vs. 58.0% in the placebo arm; HR 0.54; 95% CI, 0.31–0.96; \( P = 0.030 \)). However, given the small sample size, the Panel considered the evidence insufficient to issue a recommendation for patients on mechanical ventilation or ECMO.

References


