Clinical Management Summary

Last Updated: July 8, 2021

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.

Downloaded from https://www.covid19treatmentguidelines.nih.gov/ on 7/13/2021

Figure 1. Therapeutic Management of NonHospitalized Adults with COVID-19

All outpatients with COVID-19 who enter the health care system should have in-person or telehealth follow-up visits. Symptomatic treatments, including hydration, antipyretics, analgesics, and antitussives, can be initiated as needed.

Patients should be counseled about symptoms that warrant re-evaluation by a health care provider (e.g., new onset dyspnea, worsening dyspnea [particularly dyspnea that occurs while the patient is resting or that interferes with daily activities], mental status changes). Home resources should be assessed before patients are discharged from a clinic, urgent care center, ED, or hospital; outpatients should have access to housing, proper nutrition, a caregiver, and a device that is suitable for telehealth. If patients are discharged while they are still receiving oxygen supplementation, they should receive oximetry monitoring and close follow-up soon after discharge.

PATIENT DISPOSITION	PANEL'S RECOMMENDATIONS
Not Requiring Hospitalization or Supplemental Oxygen, As Determined by a Health Care Provider in ED or an In-Person or Telehealth Visit	Anti-SARS-CoV-2 monoclonal antibody products are recommended for outpatients with mild to moderate COVID-19 who are at high risk of disease progression, as defined by the EUA criteria (treatments are listed in alphabetical order):[a] • **Casirivimab plus imdevimab**; *or* • **Sotrovimab** At this time, the Panel **recommends against** the use of **bamlanivimab plus etesevimab** in these patients due to an increase in the proportion of potentially resistant variants **(AIII)**.[a] See text for details. The Panel **recommends against** the use of **dexamethasone** or **other systemic glucocorticoids** in the absence of another indication **(AIII)**.[b]
Discharged From Hospital Inpatient Setting in Stable Condition and Does Not Require Supplemental Oxygen	The Panel **recommends against** continuing the use of **remdesivir (AIIa)**, **dexamethasone (AIIa)**, or **baricitinib (AIIa)** after hospital discharge.
Discharged From Hospital Inpatient Setting and Requires Supplemental Oxygen *For those who are stable enough for discharge but who still require oxygen*[c]	There is insufficient evidence to recommend either for or against the continued use of remdesivir, dexamethasone, and/or baricitinib. Review the text below when considering the use of any of these agents after hospital discharge.
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*[d]	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)**. There is insufficient evidence to recommend either for or against the use of remdesivir. When considering the use of remdesivir, review the text below for further discussion. The Panel **recommends against** the use of **baricitinib** in this setting, except in a clinical trial **(AIII)**.

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

[a] In laboratory studies, some SARS-CoV-2 variants of concern or interest harbor certain mutations that are associated with reduced susceptibility to certain agents. Some regimens may be preferred in certain settings based on the degree of reduced susceptibility and the prevalence of these variants in a given region. See Anti-SARS-CoV-2 Monoclonal Antibodies and the Panel's statement on the EUAs for anti-SARS-CoV-2 monoclonal antibodies for more information. Updates on the distribution of bamlanivimab plus etesevimab are available on the HHS Bamlanivimab/Etesevimab website.

[b] 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.

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

[d] In cases where 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 (whether patients are receiving oxygen at home for the first time or are increasing their baseline oxygen requirements), pulse oximetry, and close follow-up through visiting nurse services, telehealth, or in-person clinic visits.

Key: ED = emergency department; EUA = Emergency Use Authorization; HHS = Department of Health and Human Services; the Panel = the COVID-19 Treatment Guidelines Panel; PO = orally

Downloaded from https://www.covid19treatmentguidelines.nih.gov/ on 7/13/2021

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

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS
Hospitalized but Does Not Require Supplemental Oxygen	The Panel **recommends against** the use of **dexamethasone (AIIa)** or other **corticosteroids (AIII)**.[a] There is insufficient evidence to recommend either for or against the routine use of remdesivir. For patients who are at high risk of disease progression, the use of remdesivir may be appropriate.
Hospitalized and Requires Supplemental Oxygen	Use one of the following options: • **Remdesivir**[b,c] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone**[d] **plus remdesivir**[b,c] (e.g., for patients who require increasing amounts of supplemental oxygen) **(BIII)** • **Dexamethasone**[d] (when combination therapy with remdesivir cannot be used or is not available) **(BI)**
Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	Use one of the following options: • **Dexamethasone**[d] **(AI)** • **Dexamethasone**[d] **plus remdesivir**[b,c] **(BIII)** For patients who were recently hospitalized[e] with rapidly increasing oxygen needs and systemic inflammation: • Add either **baricitinib**[f,g] **(BIIa)** or **tocilizumab**[f,h] **(BIIa)** to one of the two options above
Hospitalized and Requires IMV or ECMO	For most patients: • **Dexamethasone**[d,i] **(AI)** For patients who are within 24 hours of admission to the ICU: • **Dexamethasone**[d,i] **plus tocilizumab**[f,h] **(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

[a] Patients who are receiving dexamethasone or another corticosteroid for other indications should continue therapy for their underlying conditions as directed by their health care provider.
[b] The dose for remdesivir is 200 mg IV for one dose, followed by remdesivir 100 mg IV once daily for 4 days or until hospital discharge (unless the patient is in a health care setting that can provide acute care that is similar to inpatient hospital care). Treatment duration may be extended to up to 10 days if there is no substantial clinical improvement by Day 5.
[c] For patients who are receiving remdesivir but progress to requiring oxygen through a high-flow device, noninvasive ventilation, IMV, or ECMO, remdesivir should be continued until the treatment course is completed.
[d] The dose for dexamethasone is 6 mg IV or PO once daily for 10 days or until hospital discharge. If dexamethasone is not available, equivalent doses of other corticosteroids (e.g., prednisone, methylprednisolone, hydrocortisone) may be used. See the Corticosteroids section for more information.
[e] For example, within 3 days of hospital admission. See the Interleukin-6 Inhibitors section for more information.
[f] As there are no studies that directly compare using baricitinib and tocilizumab as treatments for COVID-19, the Panel has insufficient evidence to recommend one drug over the other. Treatment decisions should be based on local guidance, drug availability, and patient comorbidities.
[g] The dose for baricitinib is 4 mg PO once daily for 14 days or until hospital discharge (refer to Table 4c for dose modifications for patients with renal impairment). Baricitinib should be used in combination with steroids (with or without remdesivir). The combination of baricitinib plus tocilizumab has not been studied, and the Panel **recommends against** the use of this combination, except in a clinical trial **(AIII)**.
[h] The dose for tocilizumab is 8 mg/kg of actual body weight (up to 800 mg) administered as a single IV dose. The combination of tocilizumab plus baricitinib has not been studied, and the use of this combination should be avoided outside of a clinical trial. See the Interleukin-6 Inhibitors section for more information.
[i] 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.

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

Downloaded from https://www.covid19treatmentguidelines.nih.gov/ on 7/13/2021

General Management of Nonhospitalized Patients With Acute COVID-19

Last Updated: July 8, 2021

Summary Recommendations
• Management of nonhospitalized patients with acute COVID-19 should include providing supportive care, taking steps to reduce the risk of SARS-CoV-2 transmission (including isolating the patient), and advising patients on when to contact a health care provider and seek an in-person evaluation **(AIII)**. • When possible, patients with symptoms of COVID-19 should be triaged via telehealth visits before receiving in-person care. Patients with dyspnea should be referred for an in-person evaluation by a health care provider and should be followed closely during the initial days after the onset of dyspnea to assess for worsening respiratory status **(AIII)**. • Management plans should be based on a patient's vital signs, physical exam findings, risk factors for progression to severe illness, and the availability of health care resources **(AIII)**. • See Therapeutic Management of Nonhospitalized Adults With COVID-19 for specific recommendations on using pharmacologic therapy in nonhospitalized patients.
Rating of Recommendations: A = Strong; B = Moderate; C = Optional **Rating of Evidence:** I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

Introduction

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

This section focuses on the evaluation and management of:

- Adults with COVID-19 in an ambulatory care setting;
- Adults with COVID-19 following discharge from the ED; *and*
- Adults with COVID-19 following inpatient discharge.

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

Managing Patients With COVID-19 in an Ambulatory Care Setting

Approximately 80% of patients with COVID-19 have mild illness that does not warrant medical intervention or hospitalization.[2] Most patients with mild COVID-19 (defined as the absence of viral pneumonia and hypoxemia) can be managed in an ambulatory care setting or at home. Patients with

Downloaded from https://www.covid19treatmentguidelines.nih.gov/ on 7/13/2021

moderate COVID-19 (those with viral pneumonia but without hypoxemia) or severe COVID-19 (those with dyspnea, hypoxemia, or lung infiltrates >50%) need in-person evaluation and close monitoring, as pulmonary disease can progress rapidly and require hospitalization.[3]

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

Assessing the Need for In-Person Evaluation

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

All patients with dyspnea, oxygen saturation (SpO_2) ≤94% on room air at sea level (if this information is available), or symptoms that suggest higher acuity (e.g., chest pain or tightness, dizziness, confusion or other mental status changes) should be referred for an in-person evaluation by a health care provider. The criteria used to determine the appropriate clinical setting for an in-person evaluation may vary by location and institution; it may also change over time as new data and treatment options emerge. There should be a low threshold for in-person evaluation of older persons and those with medical conditions associated with 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.

Downloaded from https://www.covid19treatmentguidelines.nih.gov/ on 7/13/2021

Clinical Considerations When Managing Patients in an Ambulatory Care Setting

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

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

If an adult patient has access to a pulse oximeter at home, SpO_2 measurements can be used to help assess overall clinical status. Patients should be advised to use pulse oximeters on warm fingers rather than cold fingers for better accuracy. Patients should inform their health care provider if the value is repeatedly below 95% on room air at sea level. Pulse oximetry may not accurately detect occult hypoxemia, especially in Black patients.[3,17,18] Additionally, SpO_2 readings obtained through a mobile phone application may not be accurate enough for clinical use.[19-21] Importantly, oximetry should only be interpreted within the context of a patient's entire clinical presentation (i.e., results should be disregarded if a patient is complaining of increasing dyspnea).

Counseling Regarding the Need for Follow-Up

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

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

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

There are no fixed criteria for admitting patients with COVID-19 to the hospital; criteria may vary by region and hospital facilities. Patients with severe disease are typically admitted to the hospital, but some patients with severe disease may not be admitted due to a high prevalence of infection and limited hospital resources. In addition, patients who could receive appropriate care at home but are

Downloaded from https://www.covid19treatmentguidelines.nih.gov/ on 7/13/2021

unable to be adequately managed in their usual residential setting are candidates for temporary shelter in supervised facilities, such as a COVID-19 alternative care facility.[22] For example, patients who are living in multigenerational households or who are homeless may not be able to self-isolate and should be provided resources such as dedicated housing units or hotel rooms, when available. Unfortunately, dedicated residential care facilities for COVID-19 patients are not widely available, and community-based solutions for self-care and isolation should be explored.

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

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

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

Managing Adults With COVID-19 Following Hospital Discharge

Most patients who are discharged from the hospital setting should have a follow-up visit with a health care provider soon after discharge. Whether an in-person or 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

Downloaded from https://www.covid19treatmentguidelines.nih.gov/ on 7/13/2021

American College of Obstetricians and Gynecologists (ACOG) has developed an algorithm to aid the practitioner in evaluating and managing pregnant outpatients with laboratory-confirmed or suspected COVID-19.[23] ACOG has also published recommendations on how to use telehealth for prenatal care and how to modify routine prenatal care when necessary to decrease the risk of SARS-CoV-2 transmission to patients, caregivers, and staff.

In pregnant patients, SpO_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.[24] 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.[25] However, these monitoring strategies can be discussed on a case-by-case basis with an obstetrician. Pregnant and lactating patients should be given the opportunity to participate in clinical trials of outpatients with COVID-19 to help inform decision-making in this population.

Considerations in Children

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

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

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

References

1. Centers for Medicare & Medicaid Services. CMS announces comprehensive strategy to enhance hospital capacity amid COVID-19 surge. 2020. Available at: https://www.cms.gov/newsroom/press-releases/cms-announces-comprehensive-strategy-enhance-hospital-capacity-amid-covid-19-surge. Accessed March 3, 2021.
2. Stokes EK, Zambrano LD, Anderson KN, et al. Coronavirus disease 2019 case surveillance—United States, January 22–May 30, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69. Available at: https://www.cdc.gov/mmwr/volumes/69/wr/pdfs/mm6924e2-H.pdf.
3. Centers for Disease Control and Prevention. Interim clinical guidance for management of patients with confirmed coronavirus disease (COVID-19). 2021. Available at:

Downloaded from https://www.covid19treatmentguidelines.nih.gov/ on 7/13/2021

https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html. Accessed March 3, 2021.

4. Centers for Disease Control and Prevention. COVID-19: how to protect yourself & others. 2021. Available at: https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html. Accessed March 15, 2021.
5. Centers for Disease Control and Prevention. COVID-19: if you are sick or caring for someone. 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/. Accessed March 15, 2021.
6. Cheng A, Caruso D, McDougall C. Outpatient management of COVID-19: rapid evidence review. *Am Fam Physician*. 2020;102(8):478-486. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33064422.
7. Morrow-Howell N, Galucia N, Swinford E. Recovering from the COVID-19 pandemic: a focus on older adults. *J Aging Soc Policy*. 2020;32(4-5):526-535. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32336225.
8. Centers for Disease Control and Prevention. Coronavirus self-checker. 2021. Available at: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/coronavirus-self-checker.html. Accessed March 3, 2021.
9. Burkett E, Carpenter CR, Hullick C, Arendts G, Ouslander JG. It's time: delivering optimal emergency care of residents of aged care facilities in the era of COVID-19. *Emerg Med Australas*. 2021;33(1):131-137. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33131219.
10. Close RM, Stone MJ. Contact tracing for native americans in rural Arizona. *N Engl J Med*. 2020;383(3):e15. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32672426.
11. Centers for Disease Control and Prevention. COVID-19: what to do if you are sick. 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/steps-when-sick.html. Accessed March 15, 2021.
12. Centers for Disease Control and Prevention. COVID-19: isolate if you are sick. 2021. Available at: https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/isolation.html. Accessed March 15, 2021.
13. Cohen PA, Hall LE, John JN, Rapoport AB. The early natural history of SARS-CoV-2 infection: clinical observations from an urban, ambulatory COVID-19 clinic. *Mayo Clin Proc*. 2020;95(6):1124-1126. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32451119.
14. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061-1069. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32031570.
15. Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington state. *JAMA*. 2020;323(16):1612-1614. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32191259.
16. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020;8(5):475-481. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32105632.
17. Luks AM, Swenson ER. Pulse oximetry for monitoring patients with COVID-19 at home. Potential pitfalls and practical guidance. *Ann Am Thorac Soc*. 2020;17(9):1040-1046. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32521167.
18. Sjoding MW, Dickson RP, Iwashyna TJ, Gay SE, Valley TS. Racial bias in pulse oximetry measurement. *N Engl J Med*. 2020;383(25):2477-2478. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33326721.
19. Modi A, Kiroukas R, Scott JB. Accuracy of smartphone pulse oximeters in patients visiting an outpatient pulmonary function lab for a 6-minute walk test. *Respir Care*. 2019;64(Suppl 10). Available at: http://rc.rcjournal.com/content/64/Suppl_10/3238714.
20. Tarassenko L, Greenhalgh T. Question: should smartphone apps be used clinically as oximeters? Answer: no. 2020. Available at: https://www.cebm.net/covid-19/question-should-smartphone-apps-be-used-as-oximeters-answer-no/. Accessed March 3, 2021.
21. Jordan TB, Meyers CL, Schrading WA, Donnelly JP. The utility of iPhone oximetry apps: a comparison with standard pulse oximetry measurement in the emergency department. *Am J Emerg Med*. 2020;38(5):925-928.

Downloaded from https://www.covid19treatmentguidelines.nih.gov/ on 7/13/2021

Available at: https://www.ncbi.nlm.nih.gov/pubmed/31471076.

22. Meyer GS, Blanchfield BB, Bohmer RMJ, Mountford MB, Vanderwagen WC. Alternative care sites for the COVID-19 pandemic: the early U.S. and U.K. experience. *NEJM Catalyst*. 2020. Available at: https://catalyst.nejm.org/doi/full/10.1056/CAT.20.0224.
23. The American College of Obstetricians and Gynecologists. Outpatient Assessment and Management for Pregnant Women with Suspected or Confirmed Novel Coronavirus (COVID-19). 2020. Available at: https://www.acog.org/-/media/project/acog/acogorg/files/pdfs/clinical-guidance/practice-advisory/covid-19-algorithm.pdf. Accessed April 2, 2020.
24. The American College of Obstetricians and Gynecologists. COVID-19 FAQs for obstetrician-gynecologists, obstetrics. 2020. Available at: https://www.acog.org/clinical-information/physician-faqs/covid-19-faqs-for-ob-gyns-obstetrics. Accessed February 8, 2021.
25. Society for Maternal-Fetal Medicine. Management considerations for pregnant patients with COVID-19. 2020. Available at: https://s3.amazonaws.com/cdn.smfm.org/media/2336/SMFM_COVID_Management_of_COVID_pos_preg_patients_4-30-20_final.pdf.

Downloaded from https://www.covid19treatmentguidelines.nih.gov/ on 7/13/2021

Therapeutic Management of Nonhospitalized Adults With COVID-19

Last Updated: July 8, 2021

Figure 1 outlines the COVID-19 Treatment Guidelines Panel's (the Panel) recommendations for using therapeutic interventions outside the hospital inpatient setting. These recommendations differ depending on the patient's disposition.

Figure 1. Therapeutic Management of NonHospitalized Adults with COVID-19

All outpatients with COVID-19 who enter the health care system should have in-person or telehealth follow-up visits. Symptomatic treatments, including hydration, antipyretics, analgesics, and antitussives, can be initiated as needed.

Patients should be counseled about symptoms that warrant re-evaluation by a health care provider (e.g., new onset dyspnea, worsening dyspnea [particularly dyspnea that occurs while the patient is resting or that interferes with daily activities], mental status changes). Home resources should be assessed before patients are discharged from a clinic, urgent care center, ED, or hospital; outpatients should have access to housing, proper nutrition, a caregiver, and a device that is suitable for telehealth. If patients are discharged while they are still receiving oxygen supplementation, they should receive oximetry monitoring and close follow-up soon after discharge.

PATIENT DISPOSITION	PANEL'S RECOMMENDATIONS
Not Requiring Hospitalization or Supplemental Oxygen, As Determined by a Health Care Provider in ED or an In-Person or Telehealth Visit	Anti-SARS-CoV-2 monoclonal antibody products are recommended for outpatients with mild to moderate COVID-19 who are at high risk of disease progression, as defined by the EUA criteria (treatments are listed in alphabetical order):[a] • **Casirivimab plus imdevimab**; *or* • **Sotrovimab** At this time, the Panel **recommends against** the use of **bamlanivimab plus etesevimab** in these patients due to an increase in the proportion of potentially resistant variants **(AIII)**.[a] See text for details. The Panel **recommends against** the use of **dexamethasone** or **other systemic glucocorticoids** in the absence of another indication **(AIII)**.[b]
Discharged From Hospital Inpatient Setting in Stable Condition and Does Not Require Supplemental Oxygen	The Panel **recommends against** continuing the use of **remdesivir (AIIa)**, **dexamethasone (AIIa)**, or **baricitinib (AIIa)** after hospital discharge.
Discharged From Hospital Inpatient Setting and Requires Supplemental Oxygen *For those who are stable enough for discharge but who still require oxygen*[c]	There is insufficient evidence to recommend either for or against the continued use of remdesivir, dexamethasone, and/or baricitinib. Review the text below when considering the use of any of these agents after hospital discharge.
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*[d]	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)**. There is insufficient evidence to recommend either for or against the use of remdesivir. When considering the use of remdesivir, review the text below for further discussion. The Panel **recommends against** the use of **baricitinib** in this setting, except in a clinical trial **(AIII)**.

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

[a] In laboratory studies, some SARS-CoV-2 variants of concern or interest harbor certain mutations that are associated with reduced susceptibility to certain agents. Some regimens may be preferred in certain settings based on the degree of reduced susceptibility and the prevalence of these variants in a given region. See Anti-SARS-CoV-2 Monoclonal Antibodies and the Panel's statement on the EUAs for anti-SARS-CoV-2 monoclonal antibodies for more information. Updates on the distribution of bamlanivimab plus etesevimab are available on the HHS Bamlanivimab/Etesevimab website.

[b] 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.

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

[d] In cases where 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 (whether patients are receiving oxygen at home for the first time or are increasing their baseline oxygen requirements), pulse oximetry, and close follow-up through visiting nurse services, telehealth, or in-person clinic visits.

Key: ED = emergency department; EUA = Emergency Use Authorization; HHS = Department of Health and Human Services; the Panel = the COVID-19 Treatment Guidelines Panel; PO = orally

Downloaded from https://www.covid19treatmentguidelines.nih.gov/ on 7/13/2021

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

Anti-SARS-CoV-2 Monoclonal Antibodies

Two combination anti-SARS-CoV-2 monoclonal antibody products (bamlanivimab plus etesevimab and casirivimab plus imdevimab) and a single monoclonal antibody (sotrovimab) have been shown to reduce the risk of hospitalization and death in the outpatient setting in those with mild to moderate COVID-19 symptoms and certain risk factors for disease progression. As a result, these products have received Emergency Use Authorizations (EUAs) from the Food and Drug Administration (FDA) for the treatment of COVID-19 in these individuals, as well as in those with other risk factors for progression that have been identified in population-based studies. There are no comparative data to determine whether there are differences in clinical efficacy or safety between these products.

The Panel recommends using one of the following anti-SARS-CoV-2 monoclonal antibodies to treat outpatients with mild to moderate COVID-19 who are at high risk of clinical progression, as defined by the EUA criteria and the Panel's statement about the EUAs (treatments are listed in alphabetical order):

- **Casirivimab plus imdevimab**; *or*
- **Sotrovimab**

At this time, the Panel **recommends against** the use of **bamlanivimab plus etesevimab (AIII)** because of the increase in the proportion of the variants of concern Gamma (P.1) and Beta (B.1.351), which have reduced susceptibility to both bamlanivimab and etesevimab. See the Centers for Disease Control and Prevention COVID-19 Data Tracker website for the latest information regarding variant proportions by region in the United States. Casirivimab plus imdevimab and sotrovimab remain active against these variants.

Treatment should be started as soon as possible after the patient receives a positive result on a SARS-CoV-2 antigen test or a nucleic acid amplification test (NAAT) and within 10 days of symptom onset. For more details on the available clinical trial data for these antibodies, see Anti-SARS-CoV-2 Monoclonal Antibodies and the Panel's statement on the EUAs for anti-SARS-CoV-2 monoclonal antibodies.

Receipt of a COVID-19 vaccine should be deferred for at least 90 days in those who have received anti-SARS-CoV-2 monoclonal antibodies. This is a precautionary measure, as the antibody treatment may interfere with vaccine-induced immune responses. In people who are vaccinated and then develop COVID-19, prior receipt of a vaccine should not affect treatment decisions, including the use of and timing of treatment with monoclonal antibodies.[3]

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

Downloaded from https://www.covid19treatmentguidelines.nih.gov/ on 7/13/2021

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 RECOVERY, dexamethasone was shown to reduce mortality in hospitalized patients with COVID-19 who required supplemental oxygen. There was no observed benefit of dexamethasone in hospitalized patients who did not receive oxygen support.[4] Nonhospitalized patients who did not require supplemental oxygen were not included in this trial; thus, the safety and efficacy of corticosteroids in this population have not been established. Therefore, 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)**. Moreover, 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.

Dexamethasone was stopped at the time of hospital discharge during RECOVERY. 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. The practice of discharging inpatients who still require oxygen was likely uncommon during RECOVERY; 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 data supporting the use of corticosteroids after discharge in such cases are limited, with the main concerns being the lack of monitoring for toxicities, including, but not limited to, blood glucose control and neuropsychiatric impairment. 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 be carefully monitored for adverse events. These individuals should receive oximetry monitoring and close follow-up through telehealth, visiting nurse services, or in-person clinic visits.

In rare cases, patients with COVID-19 who require supplemental oxygen and hospital admission may need to be discharged from the emergency department (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 clinic visits.

Remdesivir

Remdesivir is currently the only drug that is approved by the FDA for the treatment of COVID-19. It is recommended for use in hospitalized patients who require supplemental oxygen. The clinical trials that evaluated the safety and efficacy of remdesivir stopped this treatment at the time of discharge from the hospital.[5-7] The Panel **recommends against** the continuation of **remdesivir (AIIa)** in hospitalized patients with COVID-19 who are stable enough for discharge and who do not require supplemental oxygen.

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. There is insufficient evidence to recommend either for or against the continued use of remdesivir after hospital discharge in patients who require supplemental oxygen. Since remdesivir can only be administered by intravenous infusion, there may be logistical issues with providing remdesivir to outpatients. If remdesivir is provided, it should only be

Downloaded from https://www.covid19treatmentguidelines.nih.gov/ on 7/13/2021

administered in health care settings that can provide a similar level of care to an inpatient hospital. These individuals should receive oximetry monitoring and close follow-up through telehealth, visiting nurse services, or in-person clinic 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 (i.e., a hospital bed or staff may not be available). There is insufficient evidence to recommend either for or against the routine use of remdesivir in this setting. If remdesivir is provided, it should only be administered in health care settings that can provide a similar level of care to an inpatient hospital. These individuals should receive oximetry monitoring and close follow-up through telehealth, visiting nurse services, or in-person clinic visits.

Baricitinib

The pivotal safety and efficacy trials for baricitinib enrolled hospitalized patients with COVID-19, and treatment was stopped at the time of hospital discharge.[8,9] The Panel **recommends against** the continuation of **baricitinib (AIIa)** in hospitalized patients with COVID-19 who are stable enough for discharge and who do not require supplemental oxygen.

There is insufficient evidence to recommend either for or against the continued use of baricitinib after hospital discharge in patients who have been discharged from the inpatient setting but who still require supplemental oxygen.

There are currently no data that assess the safety and efficacy of using baricitinib in patients who require supplemental oxygen and hospital admission, but who have been discharged from the ED due to scarce resources. Therefore, the Panel **recommends against** the use of **baricitinib** in these patients, except in a clinical trial **(AIII)**.

Other Agents That Have Been Studied or Are Under Investigation for Use in the Outpatient Management of 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 outpatient treatment of COVID-19.
- The Panel **recommends against** the use of **antibacterial therapy** (e.g., **azithromycin**, **doxycycline**) for 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** and **fluvoxamine**
  - Supplements, such as **vitamin C**, **vitamin D**, and **zinc**
- **Anticoagulants and antiplatelet therapy** should not be initiated in the outpatient setting 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 **(AIII)**. For more information, see Antithrombotic Therapy in Patients With COVID-19.
- 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 participating in clinical trials **(AIII)**.

Downloaded from https://www.covid19treatmentguidelines.nih.gov/ on 7/13/2021

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 Certain Concomitant Medications in Patients With COVID-19). **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.[10] 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.

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

1. Caputo ND, Strayer RJ, Levitan R. Early self-proning in awake, non-intubated patients in the emergency department: a single ED's experience during the COVID-19 pandemic. *Acad Emerg Med*. 2020;27(5):375-378. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32320506.
2. National Institute for Health and Care Excellence (NICE) in collaboration with NHS England and NHS Improvement. Managing COVID-19 symptoms (including at the end of life) in the community: summary of NICE guidelines. *BMJ*. 2020;369:m1461. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32312715.
3. Centers for Disease Control and Prevention. Interim clinical considerations for use of COVID-19 vaccines currently authorized in the United States. 2021. Available at: https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html. Accessed July 7, 2021.
4. Recovery Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized Patients with COVID-19. *N Engl J Med*. 2021;384(8):693-704. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32678530.
5. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of COVID-19—final report. *N Engl J Med*. 2020;383(19):1813-1826. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32445440.
6. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 days in patients with severe COVID-19. *N Engl J Med*. 2020;383(19):1827-1837. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32459919.
7. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. *JAMA*. 2020;324(11):1048-1057. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32821939.
8. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus remdesivir for hospitalized adults with COVID-19. *N Engl J Med*. 2021;384(9):795-807. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33306283.
9. Marconi VC, Ramanan AV, de Bono S, et al. Baricitinib plus standard of care for hospitalized adults with COVID-19. *medRxiv*. 2021;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.04.30.21255934v1.
10. Cazzola M, Ora J, Bianco A, Rogliani P,Matera MG. Guidance on nebulization during the current COVID-19 pandemic. *Respir Med*. 2021;176:106236. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33248363.

Downloaded from https://www.covid19treatmentguidelines.nih.gov/ on 7/13/2021

Therapeutic Management of Hospitalized Adults With COVID-19

Last Updated: July 8, 2021

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

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS
Hospitalized but Does Not Require Supplemental Oxygen	The Panel **recommends against** the use of **dexamethasone (AIIa)** or other **corticosteroids (AIII)**.[a] There is insufficient evidence to recommend either for or against the routine use of remdesivir. For patients who are at high risk of disease progression, the use of remdesivir may be appropriate.
Hospitalized and Requires Supplemental Oxygen	Use one of the following options: • **Remdesivir**[b,c] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone**[d] **plus remdesivir**[b,c] (e.g., for patients who require increasing amounts of supplemental oxygen) **(BIII)** • **Dexamethasone**[d] (when combination therapy with remdesivir cannot be used or is not available) **(BI)**
Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	Use one of the following options: • **Dexamethasone**[d] **(AI)** • **Dexamethasone**[d] **plus remdesivir**[b,c] **(BIII)** For patients who were recently hospitalized[e] with rapidly increasing oxygen needs and systemic inflammation: • Add either **baricitinib**[f,g] **(BIIa)** or **tocilizumab**[f,h] **(BIIa)** to one of the two options above
Hospitalized and Requires IMV or ECMO	For most patients: • **Dexamethasone**[d,i] **(AI)** For patients who are within 24 hours of admission to the ICU: • **Dexamethasone**[d,i] **plus tocilizumab**[f,h] **(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

[a] Patients who are receiving dexamethasone or another corticosteroid for other indications should continue therapy for their underlying conditions as directed by their health care provider.
[b] The dose for remdesivir is 200 mg IV for one dose, followed by remdesivir 100 mg IV once daily for 4 days or until hospital discharge (unless the patient is in a health care setting that can provide acute care that is similar to inpatient hospital care). Treatment duration may be extended to up to 10 days if there is no substantial clinical improvement by Day 5.
[c] For patients who are receiving remdesivir but progress to requiring oxygen through a high-flow device, noninvasive ventilation, IMV, or ECMO, remdesivir should be continued until the treatment course is completed.
[d] The dose for dexamethasone is 6 mg IV or PO once daily for 10 days or until hospital discharge. If dexamethasone is not available, equivalent doses of other corticosteroids (e.g., prednisone, methylprednisolone, hydrocortisone) may be used. See the Corticosteroids section for more information.
[e] For example, within 3 days of hospital admission. See the Interleukin-6 Inhibitors section for more information.
[f] As there are no studies that directly compare using baricitinib and tocilizumab as treatments for COVID-19, the Panel has insufficient evidence to recommend one drug over the other. Treatment decisions should be based on local guidance, drug availability, and patient comorbidities.
[g] The dose for baricitinib is 4 mg PO once daily for 14 days or until hospital discharge (refer to Table 4c for dose modifications for patients with renal impairment). Baricitinib should be used in combination with steroids (with or without remdesivir). The combination of baricitinib plus tocilizumab has not been studied, and the Panel **recommends against** the use of this combination, except in a clinical trial **(AIII)**.
[h] The dose for tocilizumab is 8 mg/kg of actual body weight (up to 800 mg) administered as a single IV dose. The combination of tocilizumab plus baricitinib has not been studied, and the use of this combination should be avoided outside of a clinical trial. See the Interleukin-6 Inhibitors section for more information.
[i] 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.

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

Downloaded from https://www.covid19treatmentguidelines.nih.gov/ on 7/13/2021

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 who are receiving dexamethasone or another corticosteroid for other indications should continue therapy for their underlying conditions as directed by their health care provider.
- There is insufficient evidence to recommend either for or against the routine use of remdesivir in these patients. The use of remdesivir may be appropriate in patients who have a high risk of disease progression.

Rationale for Recommending Against the Use of Dexamethasone or Other Corticosteroids

In RECOVERY, a multicenter, open-label trial in the United Kingdom, hospitalized patients with COVID-19 were randomized to receive either dexamethasone plus standard of care or standard of care alone (control arm).[1] In the subgroup of participants who did not require supplemental oxygen at enrollment, no survival benefit was observed for dexamethasone: 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). Please 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 this subgroup, unless the patient has another indication for corticosteroid therapy.

Rationale for the Panel's Assessment 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 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 group.[2]

In a manufacturer-sponsored, open-label randomized trial of 596 patients with moderate COVID-19, patients who received 5 days of remdesivir had higher odds of having a better clinical status on Day 11 (based on distribution on a seven-point ordinal scale) than those who received standard of care (OR 1.65; 95% CI, 1.09–2.48; $P = 0.02$). However, the difference between the arms was of uncertain clinical importance.[3]

The Solidarity trial was a large, multinational, open-label randomized controlled trial in which a 10-day course of remdesivir was compared to standard of care (control arm). About 25% of hospitalized patients in the remdesivir and control 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 in 13 of 664 patients (2.1%) in the control arm (rate ratio 0.90; 99% CI, 0.31–2.58).[4] The open-label design of this study makes it difficult to determine whether remdesivir affects recovery time as determined by duration of hospitalization, because patient discharge may have been delayed in order to complete remdesivir therapy. Please see Table 2a for additional information.

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 there may be situations in which a clinician judges that remdesivir is an appropriate treatment for a hospitalized patient with moderate disease (e.g., in cases where a person is at a particularly high risk for clinical deterioration).

Downloaded from https://www.covid19treatmentguidelines.nih.gov/ on 7/13/2021

Patients Who Require Supplemental Oxygen but Who Do Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or Extracorporeal Membrane Oxygenation

Recommendations

The Panel recommends one of the following options for these patients:

- **Remdesivir** (e.g., for patients who require minimal supplemental oxygen) **(BIIa)**;
- **Dexamethasone plus remdesivir** (e.g., for patients who require increasing amounts of oxygen) **(BIII)**; *or*
- **Dexamethasone** (when combination therapy with remdesivir cannot be used or is not available) **(BI)**.

Additional Considerations

- If dexamethasone is not available, an alternative corticosteroid such as **prednisone**, **methylprednisolone**, or **hydrocortisone** can be used **(BIII)**. See Corticosteroids for dosing recommendations.
- There is insufficient evidence to determine which patients in this group would benefit from adding baricitinib or tocilizumab to dexamethasone treatment. Some Panel members would add baricitinib or tocilizumab to a patient's dexamethasone treatment in cases where the patient has rapidly increasing oxygen needs and increased markers of inflammation but does not yet require high-flow oxygen or noninvasive ventilation.
- As there are no studies that directly compare using baricitinib and tocilizumab as treatments for COVID-19, the Panel has insufficient evidence to recommend one drug over the other. Treatment decisions should be made based on local guidance, drug availability, and patient comorbidities.

Rationale for the Use of Remdesivir

In ACTT-1, remdesivir was associated with improved time to recovery in the subgroup of participants (n = 435) who required oxygen supplementation but not high-flow oxygen, noninvasive ventilation, or mechanical ventilation (7 days for remdesivir vs. 9 days for placebo; recovery rate ratio 1.45; 95% CI, 1.18–1.79). A lower percentage of patients in the remdesivir arm than in the placebo arm progressed to requiring high-flow oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) among those who were not using these methods of oxygen delivery at baseline (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).[2]

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 patients who progressed to invasive mechanical ventilation (11.9% vs. 11.5%) or in length of hospital stay.[4] However, an open-label trial like Solidarity is less well-suited to assess time to recovery than a placebo-controlled trial. In Solidarity, 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.

Based on the results of ACTT-1, the Panel recommends **remdesivir** (without dexamethasone) as a treatment option for certain patients who require supplemental oxygen (e.g., those who require minimal

Downloaded from https://www.covid19treatmentguidelines.nih.gov/ on 7/13/2021

supplemental oxygen) **(BIIa)**. In these individuals, the hyperinflammatory state where corticosteroids might be most beneficial may not yet be present or fully developed. For more information, please see Table 2a.

Rationale for the Use of Remdesivir Plus Dexamethasone

The safety and efficacy of using remdesivir plus dexamethasone for the treatment of COVID-19 have not been rigorously evaluated in clinical trials. Despite the lack of clinical trial data, there is a theoretical rationale for combining remdesivir and dexamethasone (see the discussion of clinical trial data for remdesivir above and the discussion for dexamethasone below). 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. However, the data on clinical outcomes for patients who received this combination are currently limited.[5]

Based on the theoretical benefits of combining antiviral and anti-inflammatory effects, the Panel recommends the combination of **dexamethasone plus remdesivir** as a treatment option for patients in this group (e.g., those who require increasing amounts of supplemental oxygen) **(BIII)**.

Rationale for the Use of Dexamethasone

In RECOVERY, treatment with dexamethasone conferred a survival benefit among participants who required supplemental oxygen at enrollment. In the dexamethasone group, 23.3% of participants died within 28 days of enrollment compared with 26.2% in the standard of care arm (rate ratio 0.82; 95% CI, 0.72–0.94).[1] However, the amount of supplemental oxygen that participants were receiving and the proportions of participants who required oxygen delivery through a high-flow device or noninvasive ventilation 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 RECOVERY received concomitant remdesivir. For more information, please see the Corticosteroids section.

Some experts prefer not to use dexamethasone monotherapy in this group because of the theoretical concern that corticosteroids might slow viral clearance when they are 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.[6-8] Some studies have suggested that corticosteroids slow SARS-CoV-2 clearance, but the results to date are inconclusive.[9-13]

Rationale for the Panel's Assessment That There Is Insufficient Evidence to Determine Which Patients Would Benefit from Dexamethasone Plus Baricitinib or Tocilizumab

In COV-BARRIER (a multinational, randomized, placebo-controlled trial), 1,525 hospitalized patients with COVID-19 who had evidence of pneumonia, an elevation in one or more inflammatory markers, and an estimated glomerular filtration rate >30 mL/min/1.73 m^2 were randomized 1:1 to receive oral baricitinib 4 mg or placebo.[3] The baricitinib dose was adjusted for patients with renal impairment. There was no significant difference between the study arms in the primary endpoint of the trial, which was the proportion of patients who progressed to requiring high-flow oxygen, noninvasive ventilation, or invasive mechanical ventilation or who died by Day 28. In the subgroup of patients who required supplemental oxygen but who did not receive it through a high-flow device or mechanical ventilation (n = 962), the addition of baricitinib resulted in a lower mortality compared to those who received placebo (HR 0.72; 95% CI, 0.45–1.16; $P = 0.11$); however, this difference was not statistically significant.

Early trials that evaluated the use of tocilizumab in patients who were hospitalized with COVID-19 did

Downloaded from https://www.covid19treatmentguidelines.nih.gov/ on 7/13/2021

not show a treatment effect for tocilizumab. These trials included a high proportion of patients who were receiving conventional oxygen therapy; however, many of these trials were underpowered, and only a small proportion of patients were also receiving corticosteroids.[14-18] Although RECOVERY reported a mortality benefit for tocilizumab, the study did not identify a particular subgroup of hospitalized patients on conventional oxygen therapy who benefited most from receiving the drug.[19] Among 21,550 participants who were randomized into the RECOVERY platform trial, only 4,116 of the participants (19%) underwent a second randomization into the tocilizumab intervention arm, suggesting that the study results are generalizable only to a restricted subset of hospitalized patients. The Consolidated Standards of Reporting Trials (CONSORT) flow diagram for RECOVERY suggests that patients with clinical evidence of progressive COVID-19 were preferentially selected for the tocilizumab study.

The Panel recognizes that there may be some hospitalized patients who are receiving conventional oxygen therapy who may have progressive hypoxemia associated with significant systemic inflammation. The addition of baricitinib or tocilizumab to their standard treatment may provide a modest benefit. Nevertheless, there is insufficient evidence to clearly characterize the subgroups within this patient population who would benefit from receiving these interventions. As there are no studies that directly compare using baricitinib and tocilizumab as treatments for COVID-19, the Panel has insufficient evidence to recommend one drug over the other. Treatment decisions should be made based on local guidance, drug availability, and patient comorbidities.

Patients Who Require Delivery of Oxygen Through a High-Flow Device or Noninvasive Ventilation but Not Invasive Mechanical Ventilation or Extracorporeal Membrane Oxygenation

Recommendations

- The Panel recommends one of the following options for these patients:
  - **Dexamethasone** alone **(AI)**; *or*
  - **Dexamethasone plus remdesivir (BIII)**.
- For recently hospitalized patients (i.e., those who are within 3 days of hospital admission) who have rapidly increasing oxygen needs, require high-flow oxygen or noninvasive ventilation, and have increased markers of inflammation, add **baricitinib (BIIa)** or **tocilizumab (BIIa)** (drugs are listed alphabetically) to one of the two options above.
- 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.

Additional Considerations

- 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 have not demonstrated an increase in the frequency of infections.
- Prophylactic treatment with ivermectin should be considered for patients who are from areas where strongyloidiasis is endemic.

Using Corticosteroids

- The combination of dexamethasone and remdesivir has not been rigorously studied in clinical trials. Because there are theoretical reasons for combining these drugs, the Panel considers both dexamethasone alone and the combination of remdesivir and dexamethasone to be acceptable

Downloaded from https://www.covid19treatmentguidelines.nih.gov/ on 7/13/2021

options for treating COVID-19 in this group of patients.

- The Panel **recommends against** the use of **remdesivir alone** because it is not clear whether remdesivir confers a clinical benefit in this group of patients **(AIIa)**.
- For patients who initially received remdesivir monotherapy and progressed to requiring high-flow oxygen or noninvasive ventilation, add dexamethasone and complete the treatment course of remdesivir.
- If dexamethasone is not available, equivalent doses of other corticosteroids such as **prednisone**, **methylprednisolone**, or **hydrocortisone** may be used **(BIII)**. See Corticosteroids for more information.

Using Baricitinib and Tocilizumab

- Baricitinib or tocilizumab should only be given in combination with dexamethasone or another corticosteroid at an equivalent dose. Some clinicians may choose to assess a patient's clinical response to dexamethasone before deciding whether adding baricitinib or tocilizumab is necessary.
- Studies that directly compare using baricitinib and tocilizumab as treatments for COVID-19 are not available. Therefore, the Panel has insufficient evidence to recommend one drug over the other. Treatment decisions should be made based on local guidance, drug availability, and patient comorbidities.
- Although some patients in REMAP-CAP and RECOVERY received a second dose of tocilizumab at the discretion of their treating physicians, there is insufficient evidence to determine which patients, if any, would benefit from an additional dose of the drug.

Rationale for the Use of Dexamethasone

In RECOVERY, treatment with dexamethasone conferred a survival benefit among participants who required supplemental oxygen without invasive mechanical ventilation at enrollment: 23.3% of the participants in the dexamethasone group died within 28 days of enrollment compared with 26.2% in the standard of care arm (rate ratio 0.82; 95% CI, 0.72–0.94).[1]

Rationale for the Use of Remdesivir Plus Dexamethasone

The combination of remdesivir plus dexamethasone has not been rigorously studied in clinical trials; therefore, the safety and efficacy of this combination are unknown. The Panel recognizes that there are theoretical reasons to use this combination, as described above. Based on these theoretical considerations, the Panel considers the combination of dexamethasone plus remdesivir a treatment option for patients in this group.

Rationale for Not Recommending Remdesivir Monotherapy

In ACTT-1, there was no observed difference in time to recovery between the remdesivir and placebo groups (recovery rate ratio 1.09; 95% CI, 0.76–1.57) in the subgroup of participants who required high-flow oxygen or noninvasive ventilation at enrollment (n = 193). A post hoc analysis did not show a survival benefit for remdesivir at Day 29.[2] However, the trial was not powered to detect differences in outcomes within subgroups. The Panel **does not recommend** using remdesivir monotherapy in these patients because there is uncertainty regarding whether remdesivir alone confers a clinical benefit in this subgroup **(AIIa)**. Dexamethasone 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 delivery through a high-flow device or noninvasive ventilation, the Panel recommends initiating dexamethasone and

Downloaded from https://www.covid19treatmentguidelines.nih.gov/ on 7/13/2021

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 Recommending the Use of Baricitinib Plus Dexamethasone in Certain Hospitalized Patients

In COV-BARRIER, 1,525 hospitalized patients with COVID-19 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).[3]

There was no difference in the primary endpoint of progression to high-flow oxygen, noninvasive ventilation, invasive 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; $P = 0.18$). All-cause mortality by Day 28 was 8.1% of patients in the baricitinib arm and 13.1% in the placebo arm, resulting in a 38.2% reduction in mortality (HR 0.57; 95% CI, 0.41–0.78; nominal $P = 0.002$). Across all the prespecified baseline disease severity subgroups, mortality estimates were numerically lower among those who received baricitinib than among those who received placebo. The difference in mortality was most pronounced in the subgroup of 370 patients who were receiving high-flow oxygen or noninvasive ventilation at baseline (17.5% of patients died 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 was comparable in the baricitinib and placebo arms.

ACTT-2 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 noninvasive ventilation. Although people who were receiving corticosteroids were excluded from ACTT-2, the results of the study support the idea that baricitinib may have a clinical benefit among patients with severe COVID-19 who are not able to receive corticosteroids.[20]

Rationale for Recommending the Combination Use of Tocilizumab and Dexamethasone in Certain Hospitalized Patients

REMAP-CAP and RECOVERY, the two largest randomized controlled tocilizumab trials 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 noninvasive ventilation.[19,21] Corticosteroids were given to a majority of patients in both studies. In REMAP-CAP, a narrowly defined population of patients who were admitted to an intensive care unit (ICU) with severe to critical COVID-19 and who were exhibiting rapid respiratory decompensation were randomized to receive open-label tocilizumab or usual care alone. Compared to usual care, the use of tocilizumab reduced in-hospital mortality (28% vs. 36%) and, over 21 days of follow-up, increased the median number of days free of respiratory and cardiovascular organ support (10 days vs. 0 days; 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 specifically in patients who are experiencing rapid respiratory decompensation. In REMAP-CAP, the evidence for therapeutic benefit was strongest among recipients who had recently started receiving oxygen through a high-flow device or noninvasive ventilation; however, the lack of subgroup analyses by oxygen requirement is a notable limitation of this study.

RECOVERY also suggested a mortality benefit for tocilizumab plus dexamethasone in patients who specifically required noninvasive ventilation or high-flow oxygen. In this study, a subset of participants with hypoxemia and C-reactive protein levels ≥75 mg/L were offered enrollment into a second randomization to receive tocilizumab or usual care. Tocilizumab reduced all-cause mortality in these

Downloaded from https://www.covid19treatmentguidelines.nih.gov/ on 7/13/2021

patients; by Day 28, 29% of participants in the tocilizumab arm had died compared to 33% in the usual care arm (rate ratio 0.86; 95% CI, 0.77–0.96).

The Panel **recommends against** using tocilizumab without concomitant corticosteroids, as multiple trials have reported that the clinical benefit of tocilizumab is seen among patients who are receiving tocilizumab plus a corticosteroid (see Table 4b).

Rationale for Recommending Against Using 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.

Patients Who Require Invasive Mechanical Ventilation or Extracorporeal Membrane Oxygenation

Recommendations

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

Additional Considerations

- If dexamethasone is not available, equivalent doses of alternative corticosteroids (e.g., **prednisone**, **methylprednisolone**, **hydrocortisone**) may be used **(BIII)**.
- For patients who initially received remdesivir monotherapy and progressed to requiring invasive mechanical ventilation or ECMO, dexamethasone should be initiated and remdesivir should be continued until the treatment course is completed.
- The Panel **recommends against** the use of **remdesivir monotherapy (AIIa)**.
- 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 physicians, 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 with ivermectin should be considered for patients who are from areas where strongyloidiasis is endemic.

Rationale for the Use of Dexamethasone Monotherapy

As the disease progresses in patients with COVID-19, 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 COVID-19 and critical illness.

Dexamethasone reduces mortality in critically ill patients with COVID-19 according to a meta-analysis that aggregated seven randomized trials and included data on 1,703 critically ill patients.[22] The largest trial in the meta-analysis was the RECOVERY trial, whose subgroup of mechanically

Downloaded from https://www.covid19treatmentguidelines.nih.gov/ on 7/13/2021

ventilated patients was included.[1] For details about the meta-analysis and the RECOVERY trial, see the Corticosteroids section. Because the benefits outweigh the potential harms, the Panel recommends the use of **dexamethasone** in hospitalized patients with COVID-19 who require invasive 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. There is, however, 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.[6,7]

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 people with non-severe COVID-19 suggested that viral clearance was delayed in patients who received corticosteroids,[23] 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.[13] Given the conflicting results from observational studies and the absence 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 these drugs 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 studies, the two largest randomized controlled tocilizumab trials to date, have both reported a mortality benefit for tocilizumab among patients who experienced rapid respiratory decompensation and were recently admitted to the ICU, including those who required invasive mechanical ventilation.[19,21] REMAP-CAP enrolled patients within 24 hours of admission to the ICU. Prior trials that enrolled patients later in the ICU course and/or who received oxygen support >24 hours after ICU admission have failed to show consistent clinical benefits for tocilizumab (see Table 4b). Thus, it is unclear whether there is a clinical benefit for tocilizumab in patients who received invasive mechanical ventilation >24 hours after ICU admission. Findings from RECOVERY suggest a clinical benefit for tocilizumab plus corticosteroids among patients with rapid clinical progression who received invasive mechanical ventilation. See the 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 invasive mechanical ventilation or ECMO. During ACTT-1, 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 among participants 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 who 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 invasive mechanical ventilation or ECMO, the Panel recommends initiating dexamethasone and continuing remdesivir until

Downloaded from https://www.covid19treatmentguidelines.nih.gov/ on 7/13/2021

the treatment course is completed. Clinical trials that evaluated remdesivir categorized patients based on their severity of illness at the start of treatment with remdesivir; 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.

References

1. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with COVID-19—preliminary report. *N Engl J Med*. 2021;384(8):693-704. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32678530.
2. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of COVID-19—final report. *N Engl J Med*. 2020;383(19):1813-1826. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32445440.
3. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. *JAMA*. 2020;324(11):1048-1057. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32821939.
4. WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed antiviral drugs for COVID-19—interim WHO Solidarity Trial results. *N Engl J Med*. 2021;384(6):497-511.Available at: https://www.ncbi.nlm.nih.gov/pubmed/33264556.
5. Benfield T, Bodilsen J, Brieghel C, et al. Improved survival among hospitalized patients with COVID-19 treated with remdesivir and dexamethasone. a nationwide population-based cohort study. *Clin Infect Dis*. 2021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34111274.
6. Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid therapy for critically ill patients with Middle East respiratory syndrome. *Am J Respir Crit Care Med*. 2018;197(6):757-767. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29161116.
7. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Med*. 2006;3(9):e343. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16968120.
8. Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, Lim WS. Corticosteroids as adjunctive therapy in the treatment of influenza. *Cochrane Database Syst Rev*. 2016;3:CD010406. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26950335.
9. Chen Y, Li L. Influence of corticosteroid dose on viral shedding duration in patients with COVID-19. *Clin Infect Dis*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7454365/.
10. Li S, Hu Z, Song X. High-dose but not low-dose corticosteroids potentially delay viral shedding of patients with COVID-19. *Clin Infect Dis*. 2021;72(7):1297-1298. Available at: https://pubmed.ncbi.nlm.nih.gov/32588877/.
11. Ding C, Feng X, Chen Y, et al. Effect of corticosteroid therapy on the duration of SARS-CoV-2 clearance in patients with mild COVID-19: a retrospective cohort study. *Infect Dis Ther*. 2020;9(4):943-952. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32986226.
12. Liu J, Zhang S, Dong X, et al. Corticosteroid treatment in severe COVID-19 patients with acute respiratory distress syndrome. *J Clin Invest*. 2020;130(12):6417-6428. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33141117.
13. Spagnuolo V, Guffanti M, Galli L, et al. Viral clearance after early corticosteroid treatment in patients with moderate or severe covid-19. *Sci Rep*. 2020;10(1):21291. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33277573.
14. Veiga VC, Prats J, Farias DLC, et al. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. *BMJ*. 2021;372:n84. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33472855.
15. Salama C, Han J, Yau L, et al. Tocilizumab in patients hospitalized with COVID-19 pneumonia. *N Engl J Med*. 2021;384(1):20-30. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33332779.

Downloaded from https://www.covid19treatmentguidelines.nih.gov/ on 7/13/2021

16. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of tocilizumab in patients hospitalized with COVID-19. *N Engl J Med*. 2020;383(24):2333-2344. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33085857.
17. Salvarani C, Dolci G, Massari M, et al. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: a randomized clinical trial. *JAMA Intern Med*. 2021;181(1):24-31. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33080005.
18. Hermine O, Mariette X, Tharaux PL, et al. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: a randomized clinical trial. *JAMA Intern Med*. 2021;181(1):32-40. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33080017.
19. RECOVERY Collaborative Group, Horby PW, Pessoa-Amorim G, et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): preliminary results of a randomised, controlled, open-label, platform trial. *Lancet*. 2021;397(10285):1637-1645. Available at: https://pubmed.ncbi.nlm.nih.gov/33933206/.
20. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus remdesivir for hospitalized adults with COVID-19. *N Engl J Med*. 2021;384(9):795-807. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33306283.
21. REMAP-CAP Investigators, Gordon AC, Mouncey PR, et al. Interleukin-6 receptor antagonists in critically ill patients with COVID-19. *N Engl J Med*. 2021;384(16):1491-1502. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33631065.
22. WHO Rapid Evidence Appraisal for COVID-19 Therapies Working Group, Sterne JAC, Murthy S, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA*. 2020;324(13):1330-1341. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32876694.
23. Li Q, Li W, Jin Y, et al. Efficacy evaluation of early, low-dose, short-term corticosteroids in adults hospitalized with non-severe COVID-19 pneumonia: a retrospective cohort study. *Infect Dis Ther*. 2020;9(4):823-836. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32880102.

Downloaded from https://www.covid19treatmentguidelines.nih.gov/ on 7/13/2021