

Clinical Alignment Summary: COVID-19 Infectious Disease Treatment

The purpose of this summary is to display how clinical guidance from different organizations is aligned in this topic area.

OVERVIEW

- Remdesivir is the only Food and Drug Administration-approved drug for the treatment of COVID-19.
- Patients with moderate to severe disease or at high risk for disease progression should be offered antiviral medication (**Table 3**).
- Dexamethasone is recommended for patients who are mechanically ventilated and those on supplemental O₂ (**Table 4**)
- Avoid medications which have shown to be ineffective or harmful to patients with COVID-19 (**Table 6**).

TABLE 1. Risk factors for COVID-19 disease progression (3).

Epidemiological – Category 1	Vital Signs – Category 2	Labs – Category 3
<ul style="list-style-type: none"> ▪ Age > 50 ▪ Pre-existing pulmonary disease ▪ Chronic kidney disease ▪ Diabetes with A1c > 7.6% ▪ History of hypertension ▪ History of cardiovascular disease ▪ Obesity (BMI > 30) ▪ Use of biologics** ▪ History of transplant or other immunosuppression* including chronic corticosteroid >20 mg/d of prednisone ▪ HIV with CD4 cell count <200 or unknown** 	<ul style="list-style-type: none"> ▪ Respiratory rate > 24 breaths/min ▪ Heart rate > 125 beats/min ▪ SpO₂ ≤94% on ambient air** ▪ PaO₂/FiO₂ < 300 mmHg 	<ul style="list-style-type: none"> ▪ D-dimer > 1000 ng/mL ▪ CPK > twice upper limit of normal ▪ CRP > 100 mg/L ▪ LDH > 245 U/L ▪ Elevated troponin ▪ Absolute lymphocyte count < 0.8 ▪ Ferritin > 500 ug/L

*Not yet proven as risk factors for progression, inferred from other infections. Other factors include poverty, racism, recent cancer chemotherapy, recent surgery. (3)

**When classifying the severity of COVID-19 based on SpO₂, please note whether the hypoxemia is new (as opposed to at or near baseline) or due to other causes (such as volume overload). (3)

TABLE 2. COVID-19 disease severity

Disease Severity Categories:

A. Not hospitalized

B. Hospitalized but does not require supplemental oxygen

C. Hospitalized and requires supplemental O₂ but does not require O₂ delivery through a high-flow device, noninvasive or invasive mechanical ventilation, or ECMO

D. Hospitalized and requires O₂ through a high-flow device or noninvasive ventilation

E. Hospitalized and requires invasive mechanical ventilation or ECMO

See [NIH COVID-19 Treatment Guidelines: Therapeutic Management of Adults with COVID-19](#) (Updated 2/11/21) for specific treatment recommendations by disease severity

TABLE 3. Approved antiviral therapy

Remdesivir	<ul style="list-style-type: none"> ▪ Recommended for treatment of COVID-19 in hospitalized patients including pregnant patients with severe illness (<i>Severe illness is defined as patients with SpO₂ ≤94% on room air, and those who require supplemental oxygen, mechanical ventilation, or ECMO</i>) (1,2,3,4): In situations where supplies are limited, recommend prioritized for use in hospitalized patients with COVID-19 who require supplemental oxygen but who are not on high flow O₂, mechanically ventilated, or on ECMO (1,3,4,5), appears to demonstrate the most benefit for these patients (4). <ul style="list-style-type: none"> - Specific treatment recommendations by disease severity, Table 2 (NIH COVID-19 Treatment Guidelines: Therapeutic Management of Adults with COVID-19, Updated 2/11/21) - If a patient who is on supplemental oxygen while receiving remdesivir progresses to requiring high-flow oxygen, noninvasive or invasive mechanical ventilation, or ECMO, the course should be completed (5) - Insufficient data to recommend for or against for the treatment of patients with mild or moderate COVID-19 (1,3,5); suggest against routine use in patients without need for supplemental oxygen and SpO₂ >94% on room air (4)
FDA Approval Status	<p>Remdesivir is approved by the Food and Drug Administration (FDA) for the treatment of COVID-19 in hospitalized adult and pediatric patients (aged ≥12 years and weighing ≥40 kg). It is also available through an FDA Emergency Use Authorization (EUA) for the treatment of COVID-19 in hospitalized pediatric patients weighing 3.5 kg to <40 kg or aged <12 years and weighing ≥3.5 kg. (5)</p>
Liver and Renal Function Considerations	<p>Liver function tests and prothrombin time should be obtained in all patients before remdesivir is administered and during treatment as clinically indicated. Remdesivir may need to be discontinued if alanine transaminase (ALT) levels increase to >10 times the upper limit of normal and should be discontinued if an increase in ALT level and signs or symptoms of liver inflammation are observed. Remdesivir is not recommended for patients with eGFR <30 mL/minute. Renal function should be monitored in patients before and during remdesivir treatment as clinically indicated (3,5)</p>
Mechanism/Target	<p>RNA dependent RNA polymerase inhibitor</p>
Toxicity	<p>Nausea, vomiting, increased AST/ALT, reversible kidney injury, hypotension during infusion</p>

TABLE 4. Other recommended medications

Dexamethasone	<ul style="list-style-type: none"> • Recommended for patients who are mechanically ventilated and those on supplemental O₂ (1,2,3,4,7) <ul style="list-style-type: none"> - There are no data to support the use of dexamethasone and remdesivir in combination, but co-administration is allowable (3). The combination of remdesivir and dexamethasone has not been studied in clinical trials; however, there are theoretical reasons for combining these drugs. - Specific treatment recommendations by disease severity, Table 2 (NIH COVID-19 Treatment Guidelines: Therapeutic Management of Patients with COVID-19, Updated 12/3/20) - Presence of coinfections should be evaluated. In severe viral pneumonia caused by influenza, corticosteroid therapy appears to result in worse clinical outcomes, including secondary bacterial infection and death (1) • <u>Considerations in pregnancy:</u> <ul style="list-style-type: none"> - Given the potential benefit of decreased maternal mortality and the low risk of fetal adverse effects for this short course of therapy, recommends using dexamethasone in pregnant women with COVID-19 who are (a) mechanically ventilated or (b) who require supplemental oxygen but are not mechanically ventilated. (7) - Crosses the placenta and should be discussed with OB/Maternal-Fetal Medicine before administration. (1,2) • If dexamethasone is not available, recommends using alternative glucocorticoids such as prednisone, methylprednisolone, or hydrocortisone. (7)
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TABLE 5. Other therapies

Anti-SARS-CoV-2 Antibody Products

- Anti-SARS-CoV-2 monoclonal antibodies that target the SARS-CoV-2 spike protein and block virus entry into cells have been evaluated for the treatment of COVID-19. To date, the Food and Drug Administration (FDA) has issued Emergency Use Authorizations (EUAs) for the following anti-SARS-CoV-2 monoclonal antibodies and combinations: **bamlanivimab** alone, **bamlanivimab plus etesevimab**, and **casirivimab plus imdevimab**
 - Recommends using one of the following combination 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 (listed in alphabetical order):
 - **Bamlanivimab 700 mg plus etesevimab 1,400 mg (Alla)**; or
 - **Casirivimab 1,200 mg plus imdevimab 1,200 mg**
 - Treatment should be started as soon as possible after the patient has received a positive result on a SARS-CoV-2 antigen or nucleic acid amplification test and within 10 days of symptom onset. (8)
 - Suggests bamlanivimab/etesevimab rather than no bamlanivimab/etesevimab among ambulatory patients with mild to moderate COVID-19 at high risk for progression to severe disease. (4)
 - Recommends against the use of anti-SARS-CoV-2 monoclonal antibodies for patients who are hospitalized because of COVID-19, except in a clinical trial. However, their use should be considered for persons with mild to moderate COVID-19 who are hospitalized for a reason other than COVID-19 but who otherwise meet the EUA criteria. (8)
 - Among hospitalized patients with severe COVID-19, recommends against bamlanivimab monotherapy. (4)
 - Because clinical outcome data are limited and there are concerns regarding decreased susceptibility of variants, recommend against the use of bamlanivimab monotherapy. (4)
 - If combination products are not available, the use of bamlanivimab monotherapy can be considered for people who meet EUA criteria on a case-by-case basis. (4)
- Pregnancy: Bamlanivimab plus etesevimab should not be withheld from a pregnant individual who has a condition that poses a high risk of progression to severe COVID-19 if the clinician thinks that the potential benefit of the combination outweighs the potential risk. (8)
- Children: There are insufficient pediatric data to recommend either for or against the use of bamlanivimab plus etesevimab or other monoclonal antibody products for children with COVID-19 who are not hospitalized but who have risk factors for severe disease. Bamlanivimab plus etesevimab may be considered on a case-by-case basis for children who meet EUA criteria in consultation with a pediatric infectious disease specialist. (8)

Convalescent Plasma

- Recommended only in the context of a clinical trial. (1,3,4) When available, patients should be offered enrollment into randomized controlled trials. (1)
- Outside of clinical trial, may consider for use if severely immunocompromised, not expected to mount an antibody response (e.g., recent solid organ transplant or stem cell transplant), or at high risk for disease progression. *Exclusion*: patients who have received monoclonal antibodies for COVID-19 treatment in prior 90-days. (2)
- Insufficient clinical data to recommend either for or against use; should not be considered standard of care for treatment of patients with COVID-19. (8)

Tocilizumab

Anti-IL6 receptor Monoclonal Antibody: Tocilizumab

- Recommend the use of **tocilizumab** in combination with **dexamethasone** in certain hospitalized patients who are exhibiting rapid respiratory decompensation due to COVID-19. (6)
 - The patients included in this population are:
 - Recently hospitalized patients who have been admitted to the intensive care unit (ICU) and who require invasive mechanical ventilation, noninvasive mechanical ventilation (NIV), or high-flow nasal canula (HFNC) oxygen (>0.4 FiO₂/30 L/min of oxygen flow) (1,2,6)

Baricitinib

- Recently hospitalized patients (not in the ICU) with rapidly increasing oxygen needs who require NIV or HFNC and have significantly increased markers of inflammation (1,2,6); discussion with pulmonary critical care recommended. (1)
 - For hospitalized patients with hypoxemia who require conventional oxygen supplementation, recommends using one of the following options: remdesivir (B1a), dexamethasone plus remdesivir or dexamethasone alone. (6)
- Among hospitalized adults with progressive severe or critical COVID-19 who have elevated markers of systemic inflammation, suggests tocilizumab in addition to standard of care (i.e., steroids) rather than standard of care alone. (4)
- On November 19, 2020, the FDA issued an EUA for the use of baricitinib in combination with remdesivir in hospitalized adults and children aged ≥ 2 years with COVID-19 who require supplemental oxygen, invasive mechanical ventilation, or ECMO.
 - Insufficient data to recommend either for or against the use of baricitinib in combination with remdesivir for the treatment of COVID-19 in hospitalized patients in cases where corticosteroids can be used instead. (1,2,3,6,8)
 - In the rare circumstances where corticosteroids cannot be used, recommend using baricitinib in combination with remdesivir for the treatment of COVID-19 in hospitalized, non-intubated patients who require oxygen supplementation. (1,2,3,4,8)
- Recommend against baricitinib in the absence of remdesivir (3,6), except in a clinical trial. (8)
- Insufficient data to recommend either for or against the use of baricitinib in combination with corticosteroids for the treatment of COVID-19. Since both agents are potent immunosuppressants, there is potential for an additive risk of infection. (3,8)
- More data are needed to clarify the role of baricitinib in the management of COVID-19. Health care providers are encouraged to discuss participation in baricitinib clinical trials with their patients. (2,8)
- Should not be routinely used as data are lacking regarding whether it may be beneficial when used instead of or in combination with dexamethasone. (3)

IL-1 inhibitors: Anakinra

- Insufficient clinical data to recommend either for or against (3,6)

Intravenous Immune Globulin (IVIG)

- Insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunoglobulins (6)
- Non-SARS-CoV-2-specific intravenous immune globulin (IVIG) not recommended, except in the context of a clinical trial (1,6)
- This should not preclude the use of IVIG when it is otherwise indicated for the treatment of complications that arise during the course of COVID-19 (6), including multisystem inflammatory syndrome (3)

Interferon beta

- Recommended only in the context of a clinical trial (2)
- Insufficient clinical data to recommend either for or against for the treatment of early (i.e., <7 days from symptom onset), mild, and moderate COVID (6)

Statins

- Continue statins if already prescribed (3,7)
- For those who have a guideline indication, and if no contraindication (e.g. pregnancy), consider starting atorvastatin 40 mg daily (3)
- Statin therapy not recommended as treatment for COVID-19 outside clinical trial (7)

TABLE 6. Medications not currently recommended

Antibiotics

- Avoid routine empiric antibiotics. (1,3)
- For patients for whom antibiotics are indicated for presumptive secondary bacterial pneumonia, ceftriaxone and doxycycline preferred over azithromycin in non-pregnant patients. (3)

Other medications

- **Hydroxychloroquine/chloroquine:** Recommend against among hospitalized patients (1,3,4,5) and non-hospitalized patients, except in the context of a clinical trial (4,5)
 - Hydroxychloroquine/chloroquine should not be co-administered with remdesivir. (3)
 - Hydroxychloroquine plus azithromycin for the treatment of COVID-19 recommended against (4) except in the context of a clinical trial. (5)
- **Interferons alpha or beta:** Recommend against use for severe or critical COVID-19. (6)
- **Lopinavir/Ritonavir:** Not recommended (1,3,4,5) or considered only in the context of a clinical trial. (2,5)
- **Ivermectin** should be reserved for other FDA approved indications (1,3), or insufficient data to recommend either for or against for the treatment of COVID-19 (5).
- **Ribavirin:** Not recommended (3) or considered only in the context of a clinical trial. (2)
- **ACE inhibitors and ARB's** not recommended outside standard indications (3) or outside clinical trial. (7)
 - American Heart Association, Heart Failure Society of America, and American College of Cardiology all recommend that ACE inhibitors or ARBs be continued in people who have an indication for these medications.

Recommendations are aligned across institutions/organizations with the exceptions as marked:

SOURCES

1. [University of Washington Medicine COVID-19 Treatment Guidelines](#), Updated 3/10/21 and [University of Washington Critical Care Management for COVID-19](#), Updated 12/4/20
2. [University of California at San Francisco Adult COVID-19 Management Guidelines](#) Updated 3/24/21
3. [Massachusetts General Hospital COVID-19 Treatment Guidance](#), Updated 12/11/20
4. [Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19](#), Updated 4/5/21
5. [NIH COVID-19 Treatment Guidelines: Potential Antiviral Drugs Under Evaluation for the Treatment of COVID-19](#), Updated 2/11/21
6. [NIH COVID-19 Treatment Guidelines: Immunomodulators Under Evaluation for the Treatment of COVID-19](#), Updated 2/11/21
7. [NIH COVID-19 Treatment Guidelines: Considerations for Certain Concomitant Medications in Patients with COVID-19](#), Updated 7/30/20
8. [NIH COVID-19 Treatment Guidelines: Anti-SARS-CoV-2 Antibody Products](#), Updated 2/11/21, [Anti-SARS-CoV-2 Monoclonal Antibodies](#), Updated 2/11/21, and [The COVID-19 Treatment Guidelines Panel's Statement on the Emergency Use Authorization of anti-SARS-CoV-2 Monoclonal Antibodies for the treatment of COVID-19](#), Updated 4/8/21

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