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 medications (Table 3).
- 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).

<table>
<thead>
<tr>
<th>Epidemiological – Category 1</th>
<th>Vital Signs – Category 2</th>
<th>Labs – Category 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 55</td>
<td>Respiratory rate &gt; 24 breaths/min</td>
<td>D-dimer &gt; 1000 ng/mL</td>
</tr>
<tr>
<td>Pre-existing pulmonary disease</td>
<td>Heart rate &gt; 125 beats/min</td>
<td>CPK &gt; twice upper limit of normal</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>SpO₂ ≤94% on ambient air**</td>
<td>CRP &gt; 100 mg/L</td>
</tr>
<tr>
<td>Diabetes with A1c &gt; 7.6%</td>
<td>PaO₂/FiO₂ &lt; 300 mmHg</td>
<td>LDH &gt; 245 U/L</td>
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<tr>
<td>History of hypertension</td>
<td>Admission absolute lymphocyte count &lt; 0.8 K/ul</td>
<td>Elevated troponin</td>
</tr>
<tr>
<td>History of cardiovascular disease</td>
<td></td>
<td>Ferritin &gt; 500 ug/L</td>
</tr>
<tr>
<td>Use of biologics**</td>
<td></td>
<td></td>
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<tr>
<td>History of transplant or other immunosuppression* including chronic corticosteroid &gt;20 mg/d of prednisone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV with CD4 cell count &lt;200 or unknown**</td>
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</table>

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

See NIH COVID-19 Treatment Guidelines: Therapeutic Management of Patients with COVID-19 (Updated 12/3/20) for specific treatment recommendations by disease severity

TABLE 3. Approved antiviral therapy

Remdesivir
- Recommended for treatment of COVID-19 in hospitalized patients including pregnant patients with severe illness (Severe illness is defined as patients with SpO₂ ≤94% on room air, and those who require supplemental oxygen, mechanical ventilation, or ECMO) (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).

- Specific treatment recommendations by disease severity, Table 2 (NIH COVID-19 Treatment Guidelines: Therapeutic Management of Patients with COVID-19, Updated 12/3/20)
- 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)

**TABLE 4. Other recommended medications**

- Recommended for patients who are mechanically ventilated and those on supplemental O₂ (1,2,3,4,7)
  - 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)

- Use in pregnancy:
  - 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 mechanically ventilated or who require supplemental oxygen but who are not mechanically ventilated (7)
  - For a patient meeting criteria for steroids due to increased risk for preterm birth and due to COVID-19: start with dexamethasone for 48 hours, followed by a less potent corticosteroid for the remainder of the 10-day course to reduce fetal exposure (3)
  - For pregnant women who do not require steroids for fetal benefit and for breastfeeding women: recommend hydrocortisone, methylprednisolone, or prednisone as dexamethasone alternative. 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)

**FDA Approval Status**

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)

**Liver and Renal Function Considerations**

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)

**Mechanism/Target**

RNA dependent RNA polymerase inhibitor

**Toxicity**

Nausea, vomiting, increased AST/ALT, reversible kidney injury, hypotension during infusion
### TABLE 5. Other therapies

#### Monoclonal Antibodies

**Bamlanivimab (AKA LY-CoV555 and LY3819253)**
- On November 9, 2020, the FDA issued an EUA to make bamlanivimab available for the treatment of non-hospitalized patients with mild to moderate COVID-19 who are at high risk for progressing to severe disease and/or hospitalization (8). For high-risk criteria see: [https://www.covid19treatmentguidelines.nih.gov/statement-on-bamlanivimab-eua](https://www.covid19treatmentguidelines.nih.gov/statement-on-bamlanivimab-eua)
- At this time, there are insufficient data to recommend either for or against the use of bamlanivimab for the treatment of outpatients with mild to moderate COVID-19 (8)
- Bamlanivimab should not be considered the standard of care for the treatment of patients with COVID-19 (2,8)
- Among ambulatory patients with COVID-19, suggests against the routine use of bamlanivimab (4)
  - In patients at increased risk (as defined by the FDA EUA), bamlanivimab is a reasonable treatment option if, after informed decision-making, the patient puts a high value on the uncertain benefits and a low value on uncertain adverse events (4)

**Casirivimab plus Imdevimab Combination**
- On November 21, 2020, the FDA issued an EUA to make the casirivimab plus imdevimab combination available for the treatment of non-hospitalized patients with mild to moderate COVID-19 who are at high risk for progressing to severe disease and/or hospitalization (8). For high-risk criteria see: [https://www.covid19treatmentguidelines.nih.gov/statement-on-casirivimab-plus-imdevimab-eua](https://www.covid19treatmentguidelines.nih.gov/statement-on-casirivimab-plus-imdevimab-eua)
- At this time, there are insufficient data to recommend either for or against the use of casirivimab plus imdevimab for the treatment of outpatients with mild to moderate COVID-19 (8)
- The casirivimab plus imdevimab combination should not be considered the standard of care for the treatment of patients with COVID-19 (8)
- Health care providers are encouraged to discuss participation in SARS-CoV-2 neutralizing antibody clinical trials with patients with mild to moderate COVID-19 (8)

#### Convalescent Plasma

- Recommended only in the context of a clinical trial (1,3,4)
- 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) (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 (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)

#### 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)

#### 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)
IL-1 inhibitors: Anakinra

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

Baricitinib

- 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. (2,3,8)
  - In the rare circumstances where corticosteroids cannot be used, recommend using baricitinib in combination with remdesivir for the treatment of COVID-19 in hospitalized, nonintubated patients who require oxygen supplementation (2,3,8)
- Recommend against the use of baricitinib in the absence of remdesivir (3), 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)

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)

Hydroxychloroquine/chloroquine:
- Among hospitalized patients with COVID-19, recommend against hydroxychloroquine (1,3,4,5)
- In non-hospitalized patients, recommend against the use of chloroquine or hydroxychloroquine for the treatment of COVID-19, except in a clinical trial (4,5)
- Recommend against the use of high-dose chloroquine (600 mg twice daily for 10 days) for the treatment of COVID-19 (5)
- Chloroquine antagonizes remdesivir in vitro against RSV; chloroquine and HCQ should not be co-administered with remdesivir (3)
- The use of hydroxychloroquine plus azithromycin for the treatment of COVID-19 is not recommended, except in the context of a clinical trial (5)
- Among hospitalized patients with COVID-19, recommend against hydroxychloroquine plus azithromycin (4)

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)

Interferons alpha or beta: Recommend against use for severe or critical COVID-19 (6)

IL-6 inhibitors (Tocilizumab): Recommend against routine use (1,3,4,6); consider only in the context of a clinical trial (1,24,6)

Lopinavir/Ritonavir: Not recommended (1,3,4,5) or considered only in the context of a clinical trial (2,5)

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 11/20/20, and University of Washington Critical Care Management for COVID-19, Updated 9/14/20
2. University of California at San Francisco Adult COVID-19 Management Guidelines, 12/15/20
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 12/2/20
5. NIH COVID-19 Treatment Guidelines: Potential Antiviral Drugs Under Evaluation for the Treatment of COVID-19, Updated 1/14/21
7. NIH COVID-19 Treatment Guidelines: Considerations for Certain Concomitant Medications in Patients with COVID-19, Updated 7/30/20

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