COVID-19 Pharmacotherapy Treatment Guidance
January 11, 2022
What’s Changed this Version: January 11, 2022

Addition of Remdesivir for outpatient treatment of mild to moderate disease and for inpatient non-severe disease.
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### Overview

There are many ongoing clinical trials and data is emerging often. Use of investigational anti-COVID-19 therapeutics should be done under approved, randomized, controlled trials whenever feasible.

### Therapeutics

This information is provided to help guide treatment conversations. State mandates, medication availability/shortages, and access to Infectious Disease resources may impact some of these recommendations at given sites. As additional information becomes available, this information will be updated accordingly.

- **Prophylaxis:** See the COVID-19 Monoclonal Antibodies for Post Exposure Prophylaxis document for use of Monoclonal Antibody therapy for post-exposure prophylaxis in individuals who are at high risk for progression to severe disease. Evidence does not support any other therapy for prophylaxis against COVID-19.

- **Treatment:** Assessment of Evidence for COVID-19-Related Treatments, updated regularly, is available in the IDSA COVID-19 Guidelines, NIH COVID Treatment Guidelines and within the ASHP COVID resource center: ASHP COVID Evidence Assessment

### Table: Patient Subsets and Therapeutics

<table>
<thead>
<tr>
<th>Patient Subset</th>
<th>Therapeutics</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OUTPATIENT</strong> Mild-Moderate Disease Outpatient with confirmed COVID-19</td>
<td>Clinical observation &amp; supportive care &lt; AND &gt; For High-Risk Patients (see comments): Paxlovid &lt;OR&gt; Monoclonal Antibody (MAB) (see comments) &lt;OR&gt; Remdesivir for 3 days &lt;OR&gt; Molnupiravir (If unable to use alternative COVID-19 treatment options)</td>
<td>Patient-specific factors (e.g., symptom duration, renal function, drug interactions) as well as product availability should drive decision-making regarding choice of agent. • Paxlovid is preferred for patients without significant drug interactions or other contraindications who present within five days of symptom onset. See full Paxlovid section below. • MAB therapy is preferred in pregnancy and is the only available treatment for pediatric patients (&lt;12 years or &lt;40 kg). Only Sotrovimab should be offered in areas of high Omicron variant prevalence. See full Monoclonal Antibody section. • See full Remdesivir section below for dose, contraindications, adverse effects, monitoring, and drug interactions • Molnupiravir is not recommended as first line. It may be used for adults, nonpregnant patients, whom alternative COVID-19 treatment options (Paxlovid or MAB) are not accessible or clinically appropriate. See full Molnupiravir section.</td>
</tr>
<tr>
<td><strong>INPATIENT NON-SEVERE DISEASE</strong> Hospitalized with confirmed or suspected COVID-19 without any severe disease criteria</td>
<td>Clinical observation &amp; supportive care &lt; AND, CONSIDER &gt; Remdesivir for 1-3 days (see comments)</td>
<td>Remdesivir Comments • Consider for patients at high risk of disease progression • Duration of 3 days or until hospital discharge, whichever comes first • See full Remdesivir section below for dose, contraindications, adverse effects, monitoring, and drug interactions</td>
</tr>
<tr>
<td><strong>INPATIENT SEVERE DISEASE – NOT INTUBATED</strong> Confirmed or suspected COVID-19 plus either of the following: a. Oxygen saturation (SpO2) ≤ 94% on room air b. Requiring supplemental oxygen</td>
<td>Supportive Care &lt;AND&gt; For patients requiring supplemental oxygen: Dexamethasone 6 mg PO/IV Daily X 10 days* &lt; AND &gt; Remdesivir for 1-5 days (see comments) &lt;AND, CONSIDER &gt; Immunomodulator (IL-6 Inhibitor or Baricitinib)</td>
<td>*Corticosteroid Comments • Duration of 10 days or until hospital discharge • If dexamethasone is unavailable, equivalent doses of an alternative glucocorticoid may be used (see corticosteroid section) Remdesivir Comments • Treatment with remdesiv earlier in the course of disease has been associated with better outcomes compared to initiation after mechanical ventilation. Also refer to remdesivir comments above. Immunomodulator Comments • Consultation with Infectious Diseases and/or Critical Care is recommended prior to treatment • Immunomodulator therapy (baricitinib and tocilizumab) should not be combined • See full IL-6 Inhibitor Section for detailed patient selection, exclusion criteria, dose, adverse effects, and monitoring • See full Baricitinib Section for detailed patient selection, exclusion criteria, dose, adverse effects, and monitoring</td>
</tr>
<tr>
<td><strong>INPATIENT SEVERE DISEASE – INTUBATED/ECMO</strong> Confirmed or suspected COVID plus either of the following: a. Requiring mechanical ventilation b. Requiring extracorporeal membrane oxygenation (ECMO)</td>
<td>Supportive Care &lt; AND &gt; Dexamethasone 6 mg PO/IV Daily X 10 days* &lt; AND, CONSIDER &gt; IL-6 Inhibitor</td>
<td>IL-6 Inhibitor Comments • Consultation with Infectious Diseases and/or Critical Care is recommended prior to treatment • See full IL-6 Inhibitor Section for detailed patient selection, exclusion criteria, dose, adverse effects, and monitoring. • Other Comments: Treatment with remdesivir is not recommended for initiation after mechanical ventilation. Courses of remdesivir started prior to need for mechanical ventilation may be completed</td>
</tr>
</tbody>
</table>
THERAPY FOR MILD TO MODERATE DISEASE

- Treatment of mild to moderate COVID-19 without risk factors for disease progression are managed with supportive care.
- For patients who are at high risk of disease progression, the addition of pharmacologic therapy with either Paxlovid, Monoclonal Antibody, or Molnupiravir is recommended. Patient-specific factors (e.g., symptom duration, renal function, drug interactions) as well as product availability and local viral variant susceptibility should drive decision-making regarding choice of agent.

PATIENTS AT HIGH RISK DISEASE PROGRESSION

- Health care providers should consider the benefit-risk for an individual patient. Examples of a patient with mild-to-moderate COVID-19 at increased risk for disease progression or death is below; information about conditions can be found at the Centers for Disease Control and Prevention’s People with Certain Medical Conditions website.

Examples of Adult and Pediatric patients (including neonates) at high risk for severe disease progression:

- Older age (for example, age ≥ 65 years of age)
- Less than 1 year old (including neonates)
- Obesity or being overweight
- Pregnancy or recent pregnancy (within last 6 months)
- Chronic kidney disease
- Chronic liver disease (cirrhosis, non-alcoholic fatty liver disease, alcoholic liver disease, autoimmune hepatitis)
- Neurological disorders, including dementia
- Diabetes Mellitus (Type 1 & Type 2)
- Immunosuppressive disease or immunosuppressive treatment (including HIV, solid organ or blood stem cell transplantation)
- Cardiovascular disease (including congenital heart disease, heart failure, coronary artery disease, or cardiomyopathies) or hypertension
- Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension)
- Smokers (current and former)
- Sickle cell disease or thalassemia
- Neurodevelopmental disorders (for example, cerebral palsy, Down Syndrome) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
- Mental health disorders (mood disorders, including depression, and schizophrenia spectrum disorders)
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19)
- Tuberculosis

MOLNUPIRAVIR

- The U.S. Food and Drug Administration (FDA) has issued an EUA for the emergency use of molnupiravir for the treatment of mild-to-moderate COVID-19 in adults with positive results of direct SARS-CoV-2 viral testing who are at high risk for progressing to severe disease including hospitalization or death, presenting within 5 days of symptom onset, and for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate. For full details please refer to the Fact Sheet for Healthcare Providers: Emergency Use Authorization For Molnupiravir.
- Molnupiravir is NOT authorized:
  - For use in patients less than 18 years of age.
  - For initiation of treatment in patients requiring hospitalization due to COVID-19
    - Molnupiravir is authorized for patients hospitalized for reasons other than COVID-19 if the patient reports mild-to-moderate symptoms of COVID-19 with a confirmed with positive result. It may be appropriate to treat...
the patient with molnupiravir if the patient is also at high risk for progression to severe COVID-19 and alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate.

- For use longer than five consecutive days.
- For pre-exposure or post-exposure prophylaxis for prevention of COVID-19

**MANDATORY REQUIREMENTS FOR ADMINISTRATION OF MOLNUPIRAVIR UNDER THE EUA:**

- Mandatory prescriber requirements prior to the patient receiving molnupiravir include:
  - Review the information contained within the “Molnupiravir Fact Sheet for Patients and Caregivers” with the patient or caregiver
  - Healthcare providers must provide an electronic or hard copy of the “Molnupiravir Fact Sheet for Patients and Caregivers” and must document that it has been given to the patient or caregiver.
  - The prescribing healthcare providers must inform the patient/caregiver that:
    - Molnupiravir is an unapproved drug that is authorized for use under this Emergency Use Authorization.
    - There are no adequate, approved, available products for the treatment of COVID-19 in adults who have mild-to-moderate COVID-19 and are at high risk for progressing to severe COVID-19, including hospitalization or death.
    - Other therapeutics are currently authorized for the same use as molnupiravir.
    - For additional information on all products authorized for treatment or prevention of COVID-19, please see https://www.fda.gov/emergencypreparedness-and-response/mcm-legal-regulatory-and-policyframework/emergency-use-authorization.
    - There are benefits and risks of taking molnupiravir as outlined in the “Molnupiravir Fact Sheet for Patients and Caregivers”
    - Merck Sharp & Dohme has established a pregnancy surveillance program.
    - Females of childbearing potential should use a reliable method of contraception correctly and consistently, as applicable, for the duration of treatment and for 4 days after the last dose of molnupiravir.
    - Males of reproductive potential who are sexually active with females of childbearing potential should use a reliable method of contraception correctly and consistently during treatment and for at least 3 months after the last dose.
    - The prescribing healthcare provider and/or the provider’s designee are/is responsible for mandatory reporting of all serious adverse events and medication errors potentially related to molnupiravir within 7 calendar days from the healthcare provider’s awareness of the event. Refer to full Molnupiravir EUA for reporting requirements.
  - Prior to initiation of therapy, prescribers should complete the “Molnupiravir Checklist Tool for Prescribers”.

**MOLNUPIRAVIR CONTRAINDICATIONS AND PRECAUTIONS:**

- **Use of Molnupiravir in Pregnancy and During Lactation And In Individuals of Childbearing Potential:**
  - Molnupiravir may cause fetal harm when administered to pregnant individuals. Therefore, molnupiravir is not recommended for use during pregnancy.
  - Advise patients on need for contraception use as appropriate:
    - Females of childbearing potential treated: should use a reliable method of contraception correctly and consistently, as applicable, for the duration of treatment and for 4 days after the last dose of molnupiravir.
    - Males of reproductive potential treated: if sexually active with females of childbearing potential, should use a reliable method of contraception correctly and consistently during treatment and for at least 3 months after the last dose
  - Bone and Cartilage Toxicity: Molnupiravir is not authorized for use in patients less than 18 years of age because it may affect bone and cartilage growth.

**MOLNUPIRAVIR DOSING TABLE**

For full details please refer to the Molnupiravir EUA.

<table>
<thead>
<tr>
<th>Adult Dosing</th>
<th>Treatment of mild-moderate COVID-19 adult patients (18 years and older) at high risk of disease progression whom alternative COVID-19 treatment options (Paxlovid or Monoclonal Antibody) are not accessible or clinically appropriate, presenting within 5 days of symptom onset:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Prior to initiation of therapy, perform the mandatory requirements for administration and complete the “Molnupiravir Checklist Tool for Prescribers: Prescriber Requirements”</td>
</tr>
<tr>
<td></td>
<td>- Molnupiravir 800 mg (four x 200 mg capsules) taken orally every 12 hours for 5 days, with or without food.</td>
</tr>
</tbody>
</table>
Pediatric Dosing
- Molnupiravir is not authorized for use in patients less than 18 years

Duration
- Molnupiravir is not authorized for use for longer than 5 consecutive days because the safety and efficacy have not been established.
- If a patient requires hospitalization after starting treatment with molnupiravir, the patient may complete the full 5 day treatment course per the healthcare provider’s discretion.

Dose Adjustments
No dosage adjustment is recommended based on renal or hepatic impairment or in geriatric patients

MOLNUPIRAVIR PREGNANCY AND LACTATION CONSIDERATIONS
- Not recommended for use during pregnancy – see Contraindications and Precautions
  - Pregnancy status should be confirmed prior to initiating therapy – see “Molnupiravir Checklist Tool for Prescribers: Prescriber Requirements”
- Advise females of childbearing potential to use an effective method of contraception during treatment with molnupiravir and for 4 days after the final dose
- Advise sexually active males with partners of childbearing potential to use a reliable method of contraception during treatment and for at least 3 months after the last dose
- Breastfeeding not recommended during treatment and for 4 days after the final dose

MOLNUPIRAVIR ADVERSE REACTIONS
- Most common adverse reactions (incidence ≥ 1%) are diarrhea, nausea, and dizziness. Additional adverse events associated with molnupiravir may become apparent with more widespread use.

MOLNUPIRAVIR DRUG INTERACTIONS
- No drug interactions have been identified based on the limited available data on the emergency use of Molnupiravir authorized under this EUA. No clinical drug-drug interaction trials of molnupiravir with concomitant medications, including other treatments for mild-to-moderate COVID-19, have been conducted

SARS-COV-2 PROTEASE INHIBITOR (PAXLOVID)
- The U.S. Food and Drug Administration has issued an EUA for the emergency use of the unapproved Paxlovid which includes nirmatrelvir, a SARS-CoV-2 main protease inhibitor, co—packaged with ritonavir, an HIV-1 protease inhibitor and CYP3A inhibitor, for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct severe acute respiratory syndrome coronavirus viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.
  - NIH Treatment Guidelines recommend against HIV protease inhibitors alone (without a SARS-CoV-2 main protease inhibitor) to treat COVID-19 outside of a clinical trial.
- Paxlovid is NOT authorized:
  - For initiation of treatment of patients requiring hospitalization due to SEVERE OR CRITICAL COVID-19
    - Paxlovid is authorized for the treatment of patients hospitalized with mild-to-moderate COVID-19, such as patients admitted for monitoring of drug-drug interactions.
      - Patients requiring hospitalization due to severe or critical COVID-19 after starting treatment with Paxlovid may complete the full 5-day treatment course per the healthcare provider’s discretion
  - For use longer than five consecutive days
  - For pre-exposure or post-exposure prophylaxis for prevention of COVID-19
PAXLOVID CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

- Paxlovid is **contraindicated** with drugs that are highly dependent on CYP3A for clearance. These interactions may lead to:
  - Clinically significant adverse reactions, potentially leading to severe, life-threatening, or fatal events from greater exposures of concomitant medications
  - Clinically significant adverse reactions from greater exposures of Paxlovid.
  - Loss of therapeutic effect of Paxlovid and possible development of viral resistance and for which elevated concentrations are associated either a potential for serious and/or life-threatening reactions, or loss of efficacy.
  - **Paxlovid is CONTRAINDICATED** with the following drugs:
    - Alpha1-adrenoreceptor antagonist: alfuzosin
    - Analgesics: pethidine, piroxicam, propoxyphene
    - Antianginal: ranolazine
    - Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine
    - Anticancer drugs: apalutamide
    - Anticonvulsant: carbamazepine, phenobarbital, phenytoin
    - Anti-gout: colchicine
    - Antimycobacterials: rifampin
    - Antipsychotics: lurasidone, pimozone, clozapine
    - Ergot derivatives: dihydroergotamine, ergotamine, methylergonovine
    - Herbal products: St. John’s Wort (Hypericum perforatum)
    - HMG-CoA reductase inhibitors: lovastatin, simvastatin
    - PDE5 inhibitor: sildenafil (Revatio®) when used for pulmonary arterial hypertension (PAH)
    - Sedative/hypnotics: triazolam, oral midazolam
  - Other established and potentially significant drug interactions (see Table 1 in Paxlovid EUA for recommendations for management and monitoring with co-administration):
    - Anticancer drugs (abemaciclib, ceritinib, dasatinib, encorafenib, ibrutinib, ivosidenib, neratinib, nilotinib, venetoclax, vinblastine, vincristine)
    - Anticoagulants (warfarin, rivaroxaban)
    - Antidepressants (bupropion, trazodone)
    - Antifungals (voriconazole, ketoconazole, isavuconazonium sulfate, itraconazole)
    - Anti-HIV protease inhibitors (amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, saquinavir, tipranavir)
    - Anti-HIV (didanosine, delavirdine, efavirenz, maraviroc, nevirapine, raltegravir, zidovudine bictegravir/emtricitabine/tenofovir)
    - Anti-infective (clarithromycin, erythromycin)
    - Antimycobacterial (bedaquiline, rifabutin)
    - Antipsychotics (quetiapine)
    - Calcium channel blockers (amlodipine, diltiazem, felodipine, nicardipine, nifedipine)
    - Cardiac glycosides (digoxin)
    - Endothelin receptor antagonists (bosentan)
    - Hepatitis C direct acting antivirals (glecaprevir/pibrentasvir, ombitasvir/paritaprevir/ritonavir and dasabuvir, sofosbuvir/velpatasvir/voxilaprevir)
    - Herbal products (St John’s Wort)
    - HMG-CoA reductase inhibitors (atorvastatin, rosuvastatin)
    - Hormonal contraceptive (ethinyl estradiol)
    - Immunosuppressants (cyclosporine, tacrolimus, sirolimus)

PAXLOVID WARNINGS AND PRECAUTIONS:

- **Drug Interactions:** Nirmatrelvir and ritonavir, which comprise Paxlovid, and certain other drugs may result in potentially significant drug interactions, which may lead to serious or life-threatening adverse reactions. See contraindications above. Patients’ medications need to be screened for serious drug interactions (i.e., medication reconciliation).
• **Dosing in Patients with Renal Impairment**: Patients with estimated GFR 60 or below require dose adjustment and the dose pack should be modified by the pharmacist prior to dispensing.

• **Hepatotoxicity**: Hepatic transaminase elevations, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir.

• **HIV-1 Drug Resistance**: Paxlovid use may lead to a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection. Patients on ritonavir- or cobicistat-containing HIV or HCV regimens should continue their treatment as indicated.

### Paxlovid Dosing Table
For full details please refer to the Paxlovid EUA.

<table>
<thead>
<tr>
<th>Adult Dosing</th>
<th>Treatment of mild-moderate COVID-19 in adult and pediatric patients (12 years of age and older weighing at least 40 kg) at high risk of disease progression, within 5 days of symptom onset:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• The dosage for Paxlovid is 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) with all three tablets taken together orally twice daily for 5 days.</td>
</tr>
<tr>
<td></td>
<td>• Missed doses within 8 hours should be taken as soon as possible and normal dosing schedule should be resumed; if dose is missed by &gt;8 hours, skip the missed dose and take the next dose at the regularly scheduled time</td>
</tr>
</tbody>
</table>

| Pediatric Dosing | Paxlovid is not authorized for use in patients less than 12 years of age or less than 40 kg |

| Duration | Paxlovid is not authorized for use for longer than 5 consecutive days. Completion of the full 5-day treatment course and continued isolation in accordance with public health recommendations are important to maximize viral clearance and minimize transmission of SARS-CoV-2. |

### Dose Adjustments

**Dosing Information in Patients with Renal Impairment:**

• Paxlovid requires dose reduction in moderate renal impairment and is not recommended for use in severe renal impairment

  Dose should be adjusted as below for patients with an estimated GFR of ≤60:

  • Estimated glomerular filtration rate (eGFR) > 60 ml/min: 300 mg nirmatrelvir/100 mg ritonavir every 12 hours for five days
  • eGFR ≤60 and ≥30 mL/min: 150 mg nirmatrelvir/100 mg ritonavir every 12 hours for five days
  • eGFR <30 mL/min: Paxlovid is not recommended

• Dispense packs should be modified by the pharmacist prior to dispensing for moderate renal impairment. Please see the "[Dispensing Information for Patients with Moderate Renal Impairment](#)" EAU sheet.

**Hepatic Impairment:**

• No dosage adjustment is needed in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment.

• Paxlovid is not recommended for use in patients with severe hepatic impairment (Child-Pugh Class C)

### Paxlovid Adverse Reactions

• Serious treatment-emergent adverse events were not reported in the FDA EUA. Most common adverse reactions (incidence ≥ 1%) are dysgeusia, diarrhea, hypertension, and myalgia. Additional adverse events associated with Paxlovid may become apparent with more widespread use.

### Paxlovid Drug Interactions

• Paxlovid (nirmatrelvir co-packaged with ritonavir) is an inhibitor of CYP3A and may increase plasma concentrations of drugs that are primarily metabolized by CYP3A. Co-administration of Paxlovid with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated [see Contraindications](#). Co-administration with other CYP3A substrates may require a dose adjustment or additional monitoring.
1. Less severe but clinically meaningful drug interactions may also occur when nirmatrelvir/ritonavir is co-administered with other agents. Levels of immunosuppressive agents such as tacrolimus, cyclosporine, or sirolimus can be increased when administered with nirmatrelvir/ritonavir. Hormonal contraceptives containing ethinyl estradiol may possibly have reduced effectiveness due to lowered ethinyl estradiol levels when administered with nirmatrelvir/ritonavir. Women of childbearing potential should be counseled to use a back-up, non-hormonal method of contraception.

**MONOCLONAL ANTIBODY THERAPY PATIENT SELECTION, DOSING, AND MONITORING**

- **Treatment:** The U.S. Food and Drug Administration (FDA) has issued Emergency Use Authorizations (EUA) for three unapproved monoclonal antibody products including Sotrovimab, the combination of bamlanivimab and etesevimab, and the combination of Casirivimab and Imdevimab (REGEN-COV™) for outpatient treatment of mild to moderate (COVID-19) in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe disease and/or hospitalization.
  - Prior to treatment the parent/caregiver should be educated with the information within, and provided with the based on product administered.
  - The following information must be documented in the patient's medical record: The patient/caregiver was given the Fact Sheet, informed of alternatives to receiving monoclonal antibody, and informed that monoclonal antibodies are an unapproved drug that is authorized for use under an EUA.
- **POST-Exposure Prophylaxis:** The U.S. Food and Drug Administration (FDA) has issued Emergency Use Authorizations (EUA) for the combination of Casirivimab and Imdevimab (REGEN-COV™) and the combination of Bamlanivimab and Etesevimab for outpatient post exposure prophylaxis in certain populations. See the COVID-19 Monoclonal Antibodies for Post Exposure Prophylaxis document.
- See the Monoclonal antibodies for pediatric and neonate patients guidance for patients less than 12 years or less than 40kg.
- **PRE-Exposure Prophylaxis:** The U.S. Food and Drug Administration (FDA) has issued Emergency Use Authorizations (EUA) for the combination of tixagevimab and cilgavimab for outpatient PRE-exposure prophylaxis in certain populations. See the COVID-19 Monoclonal Antibodies for PRE-Exposure Prophylaxis document.
- The NIH and IDSA guidelines recommend use of Casirivimab and Imdevimab (REGEN-COV™) or Sotrovimab among ambulatory patients with mild to moderate COVID-19 at high risk for progression to severe disease. In people who are vaccinated and then develop COVID-19, prior receipt of vaccine should not affect treatment decisions, including the use of and timing of treatment with monoclonal antibodies.
- Circulating SARS-CoV-2 viral variants may be associated with resistance to monoclonal antibodies; please see information in the product selection information below.
- In patients admitted to the hospital for management of conditions other than treatment of COVID-19, who are diagnosed with COVID-19 and experiencing mild-to-moderate symptoms, monoclonal antibody is a reasonable treatment option if the patient meets FDA EUA for high risk. Therapy should be prescribed after informed decision-making for patients that place a high value on the uncertain benefits and a low value on uncertain adverse events.

**Limitations of authorized use:**
- Monoclonal antibody therapy is not authorized for use in patients who are hospitalized due to COVID-19, who require oxygen therapy due to COVID-19, or who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.
- Benefit of treatment with monoclonal antibody therapy has not been observed in patients hospitalized due to COVID-19. Monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

**MONOCLONAL ANTIBODY (MAB) PRODUCT SELECTION AND DOSING TABLES**

- Circulating SARS-CoV-2 viral variants are associated with resistance to monoclonal antibodies.
- Health care providers should use information on the prominent local variant proportions, information from state and local health authorities, and the Antiviral Resistance information in each of the product fact sheets to guide decisions on antibody product selection. Variant and resistance information can also be found on the IDSA Emerging Variants website.
- Local COVID-19 response teams, in collaboration with infectious disease providers, should regularly evaluate (i.e. weekly) the local variant proportions to ensure MAB product selections are appropriate for current variants.
• Sotrovimab is the only monoclonal antibody that maintains activity against the Omicron variant. In areas of high Omicron prevalence, bamlanivimab/etesevimab and casirivimab/imdevimab should not be used. If sotrovimab is unavailable, alternative treatments should be selected (see Therapeutics section).

• Bamlanivimab and etesevimab are not authorized for use in states, territories, and US jurisdictions in which the combined frequency of variants resistant to bamlanivimab and etesevimab exceeds 5%. A list of states, territories, and US jurisdictions in which bamlanivimab and etesevimab are and are not currently authorized is available on the FDA website: https://www.fda.gov/media/151719/download.
  - Review travel and contact history within 2 weeks prior to infection. Persons who have traveled to, resided in, or had close contact with an infected individual from an area where the frequency of resistant variants to bamlanivimab and etesevimab exceeds 5% should NOT receive bamlanivimab and etesevimab. Consider Casirivimab and Imdevimab (REGEN-COV™) as an alternative.

MONOCLONAL ANTIBODY CONTRAINDICATIONS AND PRECAUTIONS:
• No contraindications to therapy currently exist.
• There are limited clinical data available for monoclonal antibody therapy. Serious and unexpected adverse events may occur that have not been previously reported with bamlanivimab use.
• Monoclonal antibodies are administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.

MONOCLONAL ANTIBODY NURSING CONSIDERATIONS
Hypersensitivity Including Infusion-Related and Anaphylactic Reactions:
• There is a potential for serious hypersensitivity reaction, including anaphylaxis, with administration of monoclonal antibodies. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive therapy.
• Signs and symptoms of infusion related reactions may include fever, difficulty breathing, reduced oxygen saturation, chills, fatigue, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), chest pain or discomfort, weakness, altered mental status, nausea, headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, vasovagal reactions (e.g., pre-syncpe, syncope), dizziness and diaphoresis. If an infusion-related reaction occurs, consider slowing or stopping the infusion and administer appropriate medications and/or supportive care.

CASIRIVIMAB AND IMDEVIMAB DOSING TABLE
For full details on dose preparation and infusion times, please refer to the Casirivimab and Imdevimab (REGEN-COV™) EUA Fact Sheet for Patients, Parents and Caregivers Emergency Use Authorization (EUA) Of Casirivimab and Imdevimab (REGEN-COV™).

<table>
<thead>
<tr>
<th>Adult Dosing</th>
<th>Casirivimab 600 mg and Imdevimab 600 mg (combined total dose of 1200 mg) x 1 dose.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric Dosing</td>
<td>Treatment of high-risk pediatric patients 12 years of age and older and weighing at least 40 kg. Casirivimab and Imdevimab (REGEN-COV™) is not authorized for patients weighing less than 40 kg.</td>
</tr>
</tbody>
</table>
  - Casirivimab 600 mg and Imdevimab 600 mg (combined total dose of 1200 mg) x 1 dose. |
| Route of Administration | The intravenous route is the recommended route of administration for treatment of COVID-19. Subcutaneous injection is an alternative route of administration when IV infusion is not feasible and would lead to delay in treatment. |
| Dose Adjustments | Renal: No dosage adjustment is recommended in patients with renal impairment. Hepatic: The effect of hepatic impairment on Casirivimab and Imdevimab (REGEN-COV™) is unknown. |

BAMLANIVIMAB AND ETSEVIMAB DOSING TABLE
For full details on dose preparation and infusion times, please refer to the Bamlanivimab and Etesevimab EUA Fact Sheet for Health Care Providers. Prior to treatment the parent/caregiver should be educated with the information within, and provided with, the Fact Sheet for Patients, Parents and Caregivers for Bamlanivimab and Etesevimab.
REMDESIVIR PATIENT SELECTION, DOSING, AND MONITORING

- Remdesivir (Veklury®) is FDA approved for adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of coronavirus disease 2019 (COVID-19) requiring hospitalization.
  - Based on available clinical data, benefit with remdesivir treatment has been primarily demonstrated for patients early in the course of disease who are in the hospital requiring supplemental oxygen.
  - For hospitalized patients not requiring supplemental oxygen, remdesivir can be considered for patients at risk of disease progression. These include patients that are older (over the age of 65 years), with a BMI above 35, or who have an underlying medical condition increases the risk for severe.

- The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the unapproved emergency use of the remdesivir for pediatric patient less than 40 kg hospitalized with of suspected or laboratory confirmed coronavirus disease 2019 (COVID-19). For full details please refer to the FACT SHEET FOR HEALTH CARE PROVIDERS EMERGENCY USE AUTHORIZATION (EUA) OF VEKLURY® (remdesivir)

- If remdesivir is initiated in a PUI who subsequently tests negative by molecular PCR testing, discontinue remdesivir; consider consultation with Infectious Diseases if COVID-19 still clinically likely

- Prior to treatment for pediatric patients ages less than 12 or weight less than 40 kg the parent/caregiver should be provided information consistent with the "Fact Sheet for Patients and Parent/Caregivers. Emergency Use Authorization (EUA) Of Remdesivir For Coronavirus Disease 2019 (COVID-19)"
  - The following information must be documented in the patient’s medical record: The patient/caregiver was informed that the fact sheet, informed of alternatives to receiving remdesivir, and informed that remdesivir is an unapproved drug that is authorized for use under EUA.

REMDESIVIR CONTRAINDICATIONS AND PRECAUTIONS:

- Remdesivir should not be initiated in patients with ALT ≥ 5 times the upper limit of normal at baseline
- Accumulation of the IV vehicle sulfobutyl-ether beta-cyclodextrin sodium (SBECD) occurs in patients with renal impairment. The FDA approval does not recommend use for adult patients with eGFR less than 30 mL per minute. After consideration of risk and benefit, remdesivir can be used with caution in adults and pediatric patients with eGFR less than 30 mL per minute or in full-term neonates (≥7 days and ≤28 days old) with serum creatinine clearance ≥ 1 mg/dL.

  Considerations in pregnancy
  - No adverse embryo-fetal events seen in animal models, however there is insufficient data in humans
  - Remdesivir should be used only if benefit exceeds the potential risk to the mother and fetus.

REMDESIVIR DOSING TABLE

For full details on dose preparation, please refer to the Remdesivir Package Insert for adults, and for pediatrics the FACT SHEET FOR HEALTH CARE PROVIDERS EMERGENCY USE AUTHORIZATION (EUA) OF VEKLURY® (remdesivir)

<table>
<thead>
<tr>
<th>Adult Dosing</th>
<th>Treatment of hospitalized COVID-19 patients (Remdesivir Package Insert)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial: 200 mg IV (over 30-120 minutes) as a single dose on Day 1; Maintenance: 100 mg IV once daily up to 5 days</td>
</tr>
<tr>
<td></td>
<td><strong>Treatment of nonhospitalized patients with mild to moderate COVID-19 (Off-label use)</strong></td>
</tr>
<tr>
<td></td>
<td>Initial: 200 mg IV (over 30-120 minutes) as a single dose on Day 1; Maintenance: 100 mg IV once daily for 3 days</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pediatric Dosing</th>
<th>Treatment of hospitalized COVID-19 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients weighing 3.5 to 39.9 kg (EUA, HealthCare Provider Factsheet)</td>
</tr>
<tr>
<td></td>
<td>Must use lyophilized powder formulation</td>
</tr>
<tr>
<td></td>
<td>Initial: 5 mg/kg IV (over 30-120 minutes) as a single dose on Day 1</td>
</tr>
<tr>
<td></td>
<td>Maintenance: 2.5 mg/kg IV (over 30-120 minutes) once daily for a total duration of 5 days</td>
</tr>
</tbody>
</table>
**Remdesivir Monitoring**

- Prior to initiation, and daily during remdesivir therapy, monitor hepatic function tests (ALT, AST, bilirubin, alkaline phosphatase), prothrombin time (PT/INR) and renal function tests (serum creatinine, CrCl/eGFR). Remdesivir is not recommended in adults and pediatric patients with eGFR less than 30 mL per minute unless the potential benefit outweighs the potential risk. Consider discontinuing remdesivir if ALT levels increase to greater than 10 times the upper limit of normal. Discontinue remdesivir if ALT elevation is accompanied by signs or symptoms of liver inflammation.

- If a serious and unexpected adverse event occurs and appears to be associated with the use of remdesivir, the prescribing health care provider and/or the provider’s designee should complete and submit a [MedWatch form](https://www.fda.gov/medwatch) to FDA Remdesivir Nursing Considerations.

- Hypersensitivity Including Infusion-Related and Anaphylactic Reactions: Hypersensitivity reactions including infusion-related and anaphylactic reactions have been observed during and following administration of remdesivir. See nursing considerations below.

**Remdesivir Nursing Considerations**

- Hypersensitivity Including Infusion-Related and Anaphylactic Reactions: Hypersensitivity reactions including infusion-related and anaphylactic reactions have been observed during and following administration of remdesivir. Signs and symptoms may include hypotension, tachycardia, bradycardia, dyspnea, wheezing, angioedema, rash, nausea, vomiting, diaphoresis, and shivering. Slower infusion rates, with a maximum infusion time of up to 120 minutes, can be considered to potentially prevent these signs and symptoms. If signs and symptoms of a clinically significant hypersensitivity reaction occur, immediately discontinue administration of remdesivir and initiate appropriate treatment.

**Remdesivir Adverse Reactions**

- An adverse reaction associated with remdesivir in clinical trials in healthy adult subjects was increased liver transaminases. Additional adverse reactions associated with the drug, some of which may be serious, may become apparent with more widespread use.

- Other adverse effects with incidence ≥10%
  - Constipation (14%) [15% in placebo group]; Hypoalbuminemia (13%) [15% in placebo group]; Hypokalemia (12%) [14% in placebo group]; Anemia (12%) [15% in placebo group]; Thrombocytopenia (10%); Increased bilirubin (10%)

**Remdesivir Drug Interactions**

- Risk of Reduced Antiviral Activity When co-administered with Chloroquine or Hydroxychloroquine: coadministration of remdesivir and chloroquine phosphate or hydroxychloroquine sulfate is not recommended based on in vitro data demonstrating an antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of Remdesivir.

- In vitro, remdesivir is a substrate for drug metabolizing enzymes CYP2C8, CYP2D6, and CYP3A4, and is a substrate for Organic Anion Transporting Polypeptides 1B1 (OATP1B1) and P-glycoprotein (P-gp) transporters. In vitro, remdesivir is an inhibitor of CYP3A4, OATP1B1, OATP1B3, BSEP, MRP4, and NTCP. The clinical relevance of these in vitro assessments has not been established. Please refer to [http://www.covid19-druginteractions.org/](http://www.covid19-druginteractions.org/)

**Convalescent Plasma**

- The FDA has authorized an [Emergency Use Authorization (EUA) for emergency use of high-titer COVID-19 convalescent plasma](https://www.fda.gov/mediwatch) (CP) for the treatment of hospitalized patients with COVID-19 that are early in the course of disease or who have impaired humoral immunity. Refer to the [full EUA document](https://www.fda.gov/mediwatch) for complete details. Details on the collection, testing, labeling, and recordkeeping accompanying the use of CP is available here: [Investigational COVID-19 Convalescent Plasma Guidance for Industry](https://www.fda.gov/mediwatch). Fact sheets for Convalescent Plasma EUA have been created for both [health care providers](https://www.fda.gov/mediwatch) and [patients](https://www.fda.gov/mediwatch).
CONVALESCENT PLASMA : PATIENT SELECTION

- Despite the EUA, convalescent plasma is not recommended for treatment of immocompetent COVID-19 patients given the lack of conclusive evidence. The National Institutes of Health (NIH) Guidelines and Infectious Diseases Society of America Guidelines recommend against use for immocompetent patients.
- Given societal recommendations against use, alternative treatment availability including monoclonal antibodies, and the lack of availability to high quality COVID-19 convalescent plasma product, the use of convalescent plasma is no longer recommended.

CORTICOSTEROIDS

- The IDSA and NIH COVID-19 Treatment Guidelines recommends using dexamethasone (at a dose of 6 mg per day for up to 10 days) in patients with severe COVID-19 who require supplemental oxygen, mechanical ventilation, or ECMO. A large randomized trial, the RECOVERY trial, has reported a significant mortality benefit with dexamethasone 6 mg daily for up to 10 days in patients requiring supplemental oxygen for COVID. In a sub-group analyses of patients without hypoxia not receiving supplemental oxygen, there was no benefit and a trend toward harm with dexamethasone. Dexamethasone is not recommended for patients with non-severe COVID-19 illness, defined as a patient with a SpO2 > 94% not requiring supplemental oxygen.
- Dexamethasone has been listed on the FDA drug shortage list since February 2019 and is chronically in sporadic supply. If dexamethasone is unavailable, an equivalent total daily dose of an alternative glucocorticoid such as methylprednisolone 32 mg daily (usually divided as 16 mg BID) and prednisone 40 mg once daily may be used.
- Systemic glucocorticoids cause a dose-dependent, usually mild, hyperglycemia. Patients with diabetes mellitus or critical illness exhibit higher blood glucose levels while taking glucocorticoids, leading to increased difficulty with glycemic control. Patients receiving corticosteroids should be monitored for hyperglycemia. Clinically significant hyperglycemia that is glucocorticoid-induced are generally treated pharmacologically in the same way that they are in patients with diabetes mellitus or glucose intolerance in the absence of glucocorticoid therapy.
  - Persistent hyperglycemia is a risk factor for infection and death in critically ill patients. Glycemic control with careful monitoring of blood glucose is necessary to achieve glycemic control while avoiding hypoglycemia.

INTERLEUKIN-6 (IL-6) INHIBITORS

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for Tocilizumab for the treatment of COVID-19 in hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). However, tocilizumab is not FDA-approved for this use. Prior to treatment the parent/caregiver should be educated with the information within, and provided with, the "Fact Sheet for Patients And Parent/Caregivers Emergency Use Authorization (EUA) Of Tocilizumab For Coronavirus Disease 2019 (COVID-19)". For Coronavirus Disease 2019 (COVID-19). However, if providing this information will delay the administration of treatment to a degree that would endanger the life of a patient, the information must be provided to the parent and/or caregiver as soon as feasible after administration.

Based on the totality of evidence and recommendations from societal guidelines (IDSA and NIH):
- It is recommended that immunomodulator therapy, given in combination with corticosteroids, is considered for patients exhibiting rapid progression of respiratory failure with evidence of inflammatory mediator elevation.
  - Tocilizumab may be used in combination with dexamethasone plus remdesivir for the patients with severe disease requiring mechanical ventilation.
  - Either Tocilizumab or Baricitinib or may be used in combination with dexamethasone plus remdesivir for the patients with severe disease not requiring mechanical ventilation. Baricitinib should be avoided in patients with recent or recurrent VTE. Tocilizumab should NOT be used in combination with baricitinib.
  - Sarilumab 400 mg administered as a single intravenous infusion (infused over at least 60 min) may be used as an alternative to IV tocilizumab, only when IV tocilizumab is not available or not feasible to use.
- Treatment with the combination of an IL-6 inhibitor with corticosteroids appears to be most effective when given earlier in the course of disease (within 2 days of admission)
- We recommend AGAINST IL-6 therapy based on inflammatory markers levels alone

**IL-6 CONTRAINDICATIONS:**
- IL-6 inhibitors therapy should not be initiated for the following patients:
  - Serious Infections: do not administer tocilizumab during any other concurrent active infection
  - Tocilizumab treatment is not recommended in patients with active hepatic disease or hepatic impairment. Do not administer tocilizumab when ALT or AST are elevated above 10 times the upper limit of the normal (ULN) reference range (caution if the ALT ≥ 5 times ULN at baseline
  - Baseline platelet count of less than 50,000/mm3
  - Baseline absolute neutrophil count of less than 1,000/mm3
  - Gastrointestinal (GI) perforation – use with caution in patients who may be at increased risk

**IL-6 INHIBITOR DOSING**

<table>
<thead>
<tr>
<th>Adult Dosing</th>
<th></th>
<th>Pediatric Dosing</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tocilizumab should be administered as a single intravenous infusion (infused over at least 60 min)</td>
<td>The FDA EAU is approved for pediatric patients 2 years and older only. Tocilizumab should be administered as a single intravenous infusion (infused over at least 60 min).</td>
<td>The EAU states that if clinical signs or symptoms worsen or do not improve after the first dose, one additional infusion of tocilizumab may be administered at least 8 hours after the initial infusion.</td>
<td></td>
</tr>
<tr>
<td>Patients at or above 30 kg weight: Tocilizumab 8 mg/kg up to a maximum dose of 800 mg</td>
<td>Patients at or above 30 kg weight: Tocilizumab 8 mg/kg up to a maximum dose of 800 mg</td>
<td>There is a lack of clarity on criteria for when a repeated dose is needed.</td>
<td></td>
</tr>
<tr>
<td>Patients less than 30 kg weight: Tocilizumab 12 mg/kg</td>
<td>Patients less than 30 kg weight: Tocilizumab 12 mg/kg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Duration**
- Renal: No dose adjustment is required in elderly patients ≥65 years of age or in patients with mild or moderate renal impairment. There are no dosage adjustments provided in the EUA or manufacturer's labeling for severe renal impairment (has not been studied).
- Hepatic: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied). Do not use in patients with AST/ALT elevations >10x the upper limit of normal. Use with caution if hepatic enzymes are >5X the upper limit of normal.

**Dose Adjustments**

| Renal: No dose adjustment is required in elderly patients ≥65 years of age or in patients with mild or moderate renal impairment. There are no dosage adjustments provided in the EUA or manufacturer's labeling for severe renal impairment (has not been studied). | Hepatic: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied). Do not use in patients with AST/ALT elevations >10x the upper limit of normal. Use with caution if hepatic enzymes are >5X the upper limit of normal. |

**IL-6 INHIBITOR ADVERSE REACTIONS**
The rate of serious adverse reactions in patients receiving IL-6 inhibitors in randomized trials to date, including the REMAP-CAP trial, did not differ significantly from standard care/placebo comparators. Known adverse reactions associated with IL-6 inhibitors include (from package insert for non-COVID related indications):
- Most common adverse reactions (incidence ≥ 3%) are constipation, anxiety, diarrhea, insomnia, hypertension and nausea
- Serious Infections: Serious infections have occurred in patients receiving IL-6 Inhibitors. Do not administer tocilizumab to a patient with an active infection, including localized infection.
- Hypersensitivity: May cause hypersensitivity or anaphylaxis; Medications for the treatment of hypersensitivity reactions should be available for immediate use.
- GI perforation: Use with caution in patients at increased risk for GI perforation; perforation has been reported, typically secondary to diverticulitis.
- Hematologic effects: Neutropenia and thrombocytopenia may occur. Monitor neutrophils and platelets.
- Hepatic effects: Hepatic injury, resulting in liver transplant or death, has been reported. Monitor LFTs prior to therapy initiation and during treatment.
- Hyperlipidemia: Therapy is associated with increases in total cholesterol, triglycerides, LDL, and/or HDL; monitor ~4 to 8 weeks after initiation, then subsequently according to current guidelines.

**IL-6 INHIBITOR MONITORING**
- Prior to therapy initiation: Neutrophils, platelets, and liver function (ALT/AST, alkaline phosphatase, and total bilirubin) to evaluate for exclusion criteria. Do not initiate treatment for COVID-19 patients with baseline ALT or AST above 10x the upper limit of normal. Do not initiate treatment in patients with ANC <1,000/mm3 or platelet count <50,000/mm3.
- Monitor all patients for signs and symptoms of hypersensitivity reactions, infection (prior to, during, and after therapy); and signs and symptoms of CNS demyelinating disorders.
IL-6 INHIBITOR NURSING CONSIDERATIONS

- Hypersensitivity Reactions, Including Anaphylaxis: Hypersensitivity reactions including anaphylactic reactions have been observed during and following administration of IL-6 inhibitors. If signs and symptoms of a clinically significant hypersensitivity reaction occur, immediately discontinue administration and initiate appropriate treatment. Reactions that required treatment discontinuation included generalized erythema, rash, and urticaria. Medications for the treatment of hypersensitivity reactions should be available for immediate use.

IL-6 DRUG INTERACTIONS

- Tocilizumab may decrease the serum concentration of CYP3A4 Substrates, however a significant interaction of tocilizumab or sarilumab with either dexamethasone or hydrocortisone is not expected. Please refer to http://www.covid19-druginteractions.org/

JANUS KINASE (JAK) INHIBITOR/BARICITINIB

BARICITINIB: PATIENT SELECTION

- Either Baricitinib or Tocilizumab may be used in combination with dexamethasone plus remdesivir for the patients with severe disease not requiring mechanical ventilation who are exhibiting rapid progression of respiratory failure with evidence of inflammatory mediator elevation.
  - The adverse effect profile of each agent should be considered prior to use. Baricitinib should NOT be used in combination with tocilizumab.
- Baricitinib with or without remdesivir may be considered for hospitalized patients who require oxygen supplementation when corticosteroids cannot be used.
- Tofacitinib may be used as an alternative to baricitinib, only when baricitinib is not available.
- The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for use of baricitinib, with or without remdesivir, to treat suspected or laboratory-confirmed COVID-19 in hospitalized adults and pediatric patients 2 years or older requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). This is not an FDA-approved use of baricitinib.
  - Prior to treatment the parent/caregiver should be educated with the information
  - provided with, the "Fact Sheet for Patients And Parent/Caregivers. Emergency Use Authorization (EUA) Of Baricitinib" For Coronavirus Disease 2019 (COVID-19)"
  - The following information must be documented in the patient's medical record: The patient/caregiver was given the Fact Sheet, informed of alternatives to baricitinib, and informed that baricitinib is an approved drug that is authorized for the unapproved use under this EUA.
  - Baricitinib is FDA approved for the treatment of Rheumatoid Arthritis. Please see the package insert for more information on the FDA approved indication.

BARICITINIB CONTRAINDICATIONS AND PRECAUTIONS:

- There are no known contraindications for baricitinib. However, baricitinib is not recommended for patients who are on dialysis, have end-stage renal disease (ESRD, EGFR <15 mL/min/1.73 m2), or have acute kidney injury or for patients with known active tuberculosis. Co-existing infection can be worsened by baricitinib therapy.

BARICITINIB DOSING

<table>
<thead>
<tr>
<th>Adult Dosing</th>
<th>For adult patients with eGFR ≥60 mL/min/1.73 m2, Baricitinib 4 mg PO/GT once daily for 14 days or until hospital discharge, whichever is first.</th>
</tr>
</thead>
</table>
| Pediatric Dosing | The recommended dosage for patients 9 years of age and older is 4 mg PO/GT once daily for 14 days of total treatment or until hospital discharge, whichever is first.  
The recommended dosage for patients ages 2 years through less than 9 years of age is 2 mg PO/GT once daily for 14 days of total treatment or until hospital discharge, whichever is first.  
Baricitinib is not authorized for patients younger than 2 years of age. |
| Dose Adjustments | Dose adjustments are required for renal dysfunction, hepatic dysfunction, and drug interactions with strong OAT3 Inhibitors. For full details on dose adjustment, please refer to the "Fact Sheet for Healthcare Providers EUA Of Baricitinib For Coronavirus Disease 2019 (COVID-19)" |
BARICITINIB MONITORING, ADVERSE REACTIONS, AND DRUG INTERACTIONS

• Prior to initiation, evaluate estimated glomerular filtration rate (eGFR), liver enzymes, and complete blood count at baseline. Repeat testing is thereafter according to local patient management practice. Monitor closely when treating patients with abnormal baseline and post-baseline laboratory values.

BARICITINIB ADVERSE REACTIONS

• Serious venous thrombosis, including pulmonary embolism, and serious infections have been observed in COVID-19 patients treated with baricitinib and are known adverse drug reactions of baricitinib. Avoid use in patients with a history of VTE (deep vein thrombosis [DVT] and/or pulmonary embolism [PE]) within the last 12 weeks or have a history of recurrent (>1) VTE (DVT/PE).
• Serious Infections: Serious infections have occurred in patients receiving baricitinib. Avoid the use of baricitinib with known active tuberculosis. Consider if the potential benefits outweigh the potential risks of baricitinib treatment in patients with active serious infections other than COVID-19 or chronic/recurrent infections.
• Thrombosis: In hospitalized patients with COVID-19, prophylaxis for venous thromboembolism is recommended unless contraindicated. If clinical features of deep vein thrombosis or pulmonary embolism occur, patients should be evaluated promptly and treated appropriately.
• Hypersensitivity: If a serious hypersensitivity occurs, discontinue baricitinib while evaluating the potential causes of the reaction.
• Other adverse effects with incidence ≥10%
  • Hypoalbuminemia (13%) [15% in placebo group]; Hypokalemia (12%) [14% in placebo group]; Anemia (12%) [15% in placebo group]; Thrombocytopenia (10%); Increased bilirubin (10%)

BARICITINIB DRUG INTERACTIONS

• Vaccinations: Avoid use of live vaccines with baricitinib
• Evaluate for drug interactions with strong OAT3 Inhibitors

HYDROXYCHLOROQUINE

• Current IDSA treatment guidelines do not recommend the use of chloroquine (CQ) or hydroxychloroquine (HCQ) in hospitalized patients with COVID-19 outside of a clinical trial. NIH guidelines now recommend against use outside of a clinical trial.
• Recent data from a large randomized controlled trial showed no evidence of benefit for mortality or other outcomes such as hospital length of stay or need for mechanical ventilation of HCQ treatment in hospitalized patients with COVID-19.
• Based on the continued review of the scientific evidence available for hydroxychloroquine sulfate for the treatment of COVID-19, the FDA has revoked the Emergency Use Authorization (EUA) based on this new information and other information discussed in their memorandum.
  o Specifically, the FDA has determined that CQ and HCQ are unlikely to be effective in treating COVID-19 for the authorized uses in the EUA. Additionally, in light of ongoing serious cardiac adverse events and other serious side effects, the known and potential benefits of CQ and HCQ no longer outweigh the known and potential risks for the authorized use.

AZITHROMYCIN

• Evidence to support the combination of hydroxychloroquine with azithromycin improves clinical outcomes for treatment of COVID-19 is lacking. However, the combination of these drugs is known to increase the likelihood of QTc prolongation which can lead to life-threatening arrhythmias and sudden cardiac death.
• Because of the potential for toxicity, routine use of this combination for inpatient treatment of COVID-19 in the absence of secondary bacterial infection is not recommended.
• For outpatients the use of antimicrobial regimens, including azithromycin, are only encouraged under approved conditions for treatment of bacterial pneumonia. Routine use in COVID is not recommended.

IVERMECTIN

The NIH have found insufficient evidence to recommend either for or against the use of ivermectin for the treatment of COVID-19. The IDSA panel suggests against ivermectin use outside of the context of a clinical trial. Current evidence with
ivermectin has incomplete data or flawed designs, thus both the NIH panel and IDSA recommend well-designed, adequately powered studies to determine the safety and efficacy of ivermectin to treat COVID-19. A randomized trial of ivermectin in outpatients with mild disease did not significantly improve the time to resolution of symptoms or prevent the need for medical care. The FDA issued a warning in April 2020 that ivermectin intended for use in animals should not be used to treat COVID-19 in humans.

**CONSIDERATIONS FOR USING CONCOMITANT MEDICATIONS IN PATIENTS WITH COVID-19**

Patients with COVID-19 who are receiving concomitant medications (e.g., angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], HMG-CoA reductase inhibitors [statins], systemic or inhaled corticosteroids, nonsteroidal anti-inflammatory drugs, acid-suppressive therapy) for underlying medical conditions should not discontinue these medications during acute management of COVID-19 unless discontinuation is otherwise warranted by their clinical condition.

**COVID AND CO-INFECTION**

Although the exact incidence of co-infection with bacterial pathogens among patients with COVID-19 is unknown, current data suggests it is uncommon (<5%). Empiric antibiotic therapy in patients with confirmed COVID is not recommended in the absence of highly suspected or confirmed bacterial co-infection.

**MANAGEMENT OF INFLUENZA CO-INFECTION**

At times of co-circulation of influenza and COVID, hospitalized patients should be started on empiric treatment for influenza with oseltamivir as soon as possible, then antiviral treatment can be tailored based on influenza and COVID testing results. For patients with influenza and COVID co-infection, consultation with an Infectious Disease is recommended. Given the benefit of dexamethasone on reducing mortality for patients with severe COVID disease, use should be considered along with the risks and benefits in a co-infected patient. The role of dual antiviral therapy is unknown, but the combination of oseltamivir and remdesivir is not expected to be detrimental.

**RESPIRATORY TREATMENTS**

Inhaled medications can be delivered either by Metered Dose Inhalers (MDIs) or by nebulization; when delivered by nebulization, these can be aerosol generating. For COVID positive or patients suspected to have COVID, the use of MDIs is preferred when / if available. Collaboration and communication between physician, nursing, respiratory and pharmacy colleagues is necessary to reduce the risk of aerosolizing respiratory secretions induced through nebulization. Please refer to the COVID-19 Patients and Inhaled Respiratory Meds and ED and Urgent Care Inhaled Respiratory Medications for COVID Patients documents on the Trinity Health COVID Resource page.

**PATIENT POSITIONING**

- For non-intubated patients, please see the "Prone Positioning for the Non-intubated Patient" reference on the Trinity Health COVID site.
- For intubated patients, please see the guidance for "Prone Positioning of the Mechanically Ventilated Patient"

**USE OF NEUROMUSCULAR BLOCKER AGENTS AND CONSERVATION**

Neuromuscular blockade (NMBA) is implemented when needed to facilitate mechanical ventilation for treatment of moderate or severe acute respiratory distress syndrome (ARDS). The historical supply shortages with these agents has been augmented by the surge in demand due to treatment of COVID-19. Conservation methods are necessary to avoid complete exhaustion of drug supply.

The Society of Critical Care Medicine (SCCM) does not recommend routine use of continuous infusion of neuromuscular blockade for all mechanically ventilated patients or for treatment of mild ARDS. For mechanically ventilated patients and with moderate to severe ARDS, the recommendation is as follows:

SCCM Recommendations:
1. For mechanically ventilated adults with COVID-19 and moderate to severe ARDS: We suggest using, as needed, intermittent boluses of neuromuscular blocking agents (NMBA), over continuous NMBA infusion, to facilitate protective lung ventilation (weak recommendation, low-quality evidence).

2. In the event of persistent ventilator dyssynchrony, the need for ongoing deep sedation, prone ventilation, or persistently high plateau pressures, we suggest using a continuous NMBA infusion for up to 48 hours (weak recommendation, low-quality evidence).

Below are the available Trinity Health Formulary Nondepolarizing NMBA agents, suggested dosing, and dose considerations:

<table>
<thead>
<tr>
<th>NMBA</th>
<th>Onset of Action (MIN)</th>
<th>Duration after INITIAL dose (MIN)</th>
<th>Usual Dose Range#</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisatracurium</td>
<td>1.5-2</td>
<td>20-35</td>
<td>Intermittent bolus dosing: 0.1 to 0.2 mg/kg/dose. Continuous infusion: Initial rate of 3 mcg/kg/min; Usual dose range of 1-10 mcg/kg/min</td>
<td></td>
</tr>
<tr>
<td>Vecuronium</td>
<td>2.3-3</td>
<td>20-40</td>
<td>Intermittent bolus dosing: 0.1 to 0.2 mg/kg/dose. Continuous infusion: Initial rate of 0.8 mcg/kg/minute; Usual dose range 0.8 to 1.7 mcg/kg/minute</td>
<td>Drug elimination varies based on renal and hepatic function.</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>1-2</td>
<td>22-67 (dose dependent)</td>
<td>Intermittent bolus dosing: 50 mg initial dose followed by 25 mg dose as needed. Continuous infusion: Initial rate of 8 mcg/kg/min; Usual dose range 8-12 mcg/kg/min</td>
<td>Vagolytic action can cause dose-dependent tachycardia.</td>
</tr>
</tbody>
</table>

**USE OF NMBA FOR COVID RECOMMENDATIONS:**

1. Implement conservation strategies to mitigate NMBA drug supply exhaustion including:
   a. Limit use of NMBA agents for patients with Severe ARDS (P/F <= 100) or who have failed prone ventilation
   b. Attempt intermittent boluses prior to continuous infusion when appropriated based on SCCM recommendations criteria
      i. Recommend 24 hours of intermittent dosing use prior to converting to continuous infusions
      ii. Local assessment with pharmacy regarding medication supply, available presentations, and dose dispensing should occur with bolus dose strategy to minimize waste
   c. If continuous infusion of a NMBA is required, use the lowest dose to achieve clinical goal and reassess the need for infusion at least twice a day. If train of 4 (TOF) monitoring is used, discontinue infusion if TOF reaches 0/4 and reassess need for infusion.
      i. For obese patients (body mass index (BMI) ≥ 30 kg/m2), use ideal body when calculating NMBA doses

2. Use succinylcholine preferentially, when appropriate, for rapid sequence intubations (RSI) to preserve rocuronium supply. Ensure that a NMBA supply is available for emergent surgeries (succinylcholine or rocuronium).

3. Critical care colleagues should familiarize themselves with alternative agents, dosing, and pharmacodynamic profile in preparation for a potential need to shift to these agents based on availability. Atracurium and Pancuronium are non-formulary alternative NMBA agents. Listed below are the suggested dosing and dose considerations:

<table>
<thead>
<tr>
<th>NMBA</th>
<th>Onset of Action (MIN)</th>
<th>Duration after INITIAL dose (MIN)</th>
<th>Usual Dose Range#</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atracurium</td>
<td>2-3</td>
<td>20-35</td>
<td>Intermittent bolus dosing: 0.4 to 0.5 mg/kg/dose. Continuous infusion: 4 to 20 mcg/kg/minute</td>
<td>Can cause histamine release, however clinical effects unlikely. Histamine release can be reduced by slowing the rate of administration.</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>2-3</td>
<td>60-100</td>
<td>Intermittent bolus dosing: 0.06 to 0.1 mg/kg/dose. Continuous infusion: 0.8 to 2 mcg/kg/minute</td>
<td>Avoid, if possible, if history of coronary artery disease. Vagolytic action and sympathetic stimulation can cause dose dependent tachycardia. Long acting agent. Dose adjustment in renal impairment.</td>
</tr>
</tbody>
</table>
SPECIAL CONSIDERATIONS IN PREGNANCY

For detailed information, please see the guidance from the National Institutes of Health (NIH), the Centers for Disease Control and Prevention, the American College of Obstetricians and Gynecologists, and the Society for Maternal-Fetal Medicine on the management of pregnant patients with COVID-19. This section summarizes key considerations regarding the management of COVID-19 in pregnancy.

- If hospitalization for COVID-19 is indicated for a pregnant patient, care should be provided in a facility that can conduct maternal and fetal monitoring, when appropriate.
- Management of COVID-19 in pregnant patients should include:
  - Fetal and uterine contraction monitoring based on gestational age, when appropriate
  - Individualized delivery planning
  - Providers should treat pregnant COVID positive patients in collaboration with Maternal Fetal Medicine specialists.
    - A multispecialty, team-based approach that may include consultation with obstetric, maternal-fetal medicine, infectious disease, pulmonary-critical care, and pediatric specialists, as appropriate
- Fetal monitoring should be determined on a case-by-case basis using gestational age and clinical judgement.
- In general, the therapeutic management of pregnant patients with COVID-19 should be the same as for nonpregnant patients.
  - Pregnant or lactating patients with COVID-19 and their clinical teams should discuss the use of investigational drugs or drugs that are approved for other indications as treatments for COVID-19. During this shared decision-making process, the patient and the clinical team should consider the safety of the medication for the pregnant or lactating individual and the fetus and the severity of maternal disease.

OXYGENATION GOALS AND PRONING IN PREGNANCY

In pregnant patients, SpO2 should be maintained at 95% or above on room air at sea level; therefore, the threshold for monitoring pregnant patients in an inpatient setting may be lower than in nonpregnant patients. Consult with a Maternal Fetal Medicine specialist prior to proning a pregnant patient.

COVID-19 PHARMACOTHERAPY IN PREGNANCY

Summary of COVID-19 pharmacotherapy treatment options in pregnant patients:

- Monoclonal Antibody Therapy, Corticosteroids, and Remdesivir should be used in same manner for the therapeutic management of patients with COVID-19 regardless of pregnancy status
- Paxlovid has no human data to evaluate for a drug-associated risk of adverse maternal or fetal outcomes. The decision to use Paxlovid during pregnancy should be a collaborative effort between pregnant individuals and their health care providers, and the decision-making process should include a discussion of the potential risks and benefits.
- Molnupiravir is NOT recommended for use during pregnancy
- The decision to use IL-6 inhibitors (Tocilizumab or Sarilumab) or JAK inhibitors (Baricitinib or Tofacitinib) during pregnancy should be a collaborative effort between pregnant individuals and their health care providers, and the decision-making process should include a discussion of the potential risks and benefits.

Please see below for further information on the considerations for specific therapeutics for COVID treatment in pregnancy (summarized from NIH guidance):

MONOCLONAL ANTIBODY CONSIDERATIONS IN PREGNANCY

The use of monoclonal antibody therapy can be considered for pregnant people with COVID-19, especially those who have additional risk factors for severe disease (see the EUA criteria for the use of these products above). As immunoglobulins, authorized monoclonal antibody therapy would be expected to cross the placenta. There are no pregnancy-specific data on
the use of these products; however, other immunoglobin products have been safely used in pregnant people when their use is indicated. Therefore, authorized monoclonal antibody therapy should not be withheld in the setting of pregnancy. When possible, pregnant and lactating people should be included in clinical trials that are evaluating the use of monoclonal antibody therapy for the treatment and/or prevention of COVID-19.

**CORTICOSTEROID CONSIDERATIONS IN PREGNANCY**

A short course of betamethasone or dexamethasone, which are known to cross the placenta, is routinely used to decrease neonatal complications of prematurity in women with threatened preterm delivery. Given the potential benefit of decreased maternal mortality and the low risk of fetal adverse effects for a short course of dexamethasone therapy, dexamethasone for hospitalized pregnant patients with COVID-19 who require supplemental oxygen or who are mechanically ventilated. However, for pregnant patients being treated for COVID where delivery is being considered and fetal lung maturity is a concern, dosing regimen should be modified to dexamethasone 6mg IM every 12 hours x 48 hours (4 doses) then dexamethasone 6 mg daily for next 8 days (10 days total treatment).

**REMDESIVIR CONSIDERATIONS IN PREGNANCY**

Pregnant patients were excluded from the clinical trials that evaluated the safety and efficacy of remdesivir for the treatment of COVID-19, but preliminary reports of remdesivir use in pregnant patients from the remdesivir compassionate use program are reassuring. Among 86 pregnant and postpartum hospitalized patients with severe COVID-19 who received compassionate use remdesivir, the therapy was well tolerated, with a low rate of serious adverse events. Remdesivir should not be withheld from pregnant patients if it is otherwise indicated.”

**INTERLEUKIN-6 INHIBITORS (TOCILIZUMAB OR SARILUMAB) CONSIDERATIONS IN PREGNANCY**

There are insufficient data to determine whether there is a tocilizumab-associated risk for major birth defects or miscarriage. mAbs are actively transported across the placenta as pregnancy progresses (with the greatest transfer occurring during the third trimester), and this may affect immune responses in utero in the exposed fetus. Given the paucity of data, current recommendations advise against the use of tocilizumab during pregnancy. The decision to use tocilizumab during pregnancy should be a collaborative effort between pregnant individuals and their health care providers, and the decision-making process should include a discussion of the potential risks and benefits.

**JAK INHIBITORS (BARICITINIB OR TOFACITINIB) CONSIDERATIONS IN PREGNANCY**

There is a paucity of data on the use of Baricitinib (JAK inhibitors) in pregnancy. As small molecule-drugs, JAK inhibitors are likely to pass through the placenta, and therefore fetal risk cannot be ruled out. Decisions regarding the administration of JAK inhibitors must include shared decision-making between the pregnant individual and their health care provider, considering potential maternal benefit and fetal risks. Factors that may weigh into the decision-making process include maternal COVID-19 severity, comorbidities, and gestational age. Pregnancy registries provide some outcome data on tofacitinib use during pregnancy for other conditions (e.g., ulcerative colitis, rheumatoid arthritis, psoriasis). Among the 33 cases reported, pregnancy outcomes were similar to those among the general population.

**PAXLOVID CONSIDERATIONS IN PREGNANCY AND LACTATION**

- There are no available human data on the use of nirmatrelvir during pregnancy to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.
  - In an animal evaluation (rabbits) with nirmatrelvir, reduced fetal body weights following administration of nirmatrelvir at approximately 10 times higher than clinical exposure at the authorized human dose of PAXLOVID. No other adverse developmental outcomes were observed in animal reproduction studies.
- Published observational studies on ritonavir use in pregnant women have not identified an increase in the risk of major birth defects. Published studies with ritonavir are insufficient to identify a drug-associated risk of miscarriage.
- There are no available data on the presence of nirmatrelvir in human or animal milk, the effects on the breastfed infant, or the effects on milk production. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.
MOLNUPIRAVIR CONSIDERATIONS IN PREGNANCY AND LACTATION

- Not recommended for use during pregnancy – see Molnupiravir Contraindications and Precautions
  - Pregnancy status should be confirmed prior to initiating therapy – see “Molnupiravir Checklist Tool for Prescribers: Prescriber Requirements”
- Advise females of childbearing potential to use an effective method of contraception during treatment with molnupiravir and for 4 days after the final dose
- Advise sexually active males with partners of childbearing potential to use a reliable method of contraception during treatment and for at least 3 months after the last dose
- Breastfeeding not recommended during treatment and for 4 days after the final dose

ANTICOAGULATION AND COVID RELATED COAGULOPATHY GUIDANCE

- Patients infected with COVID-19 are at increased risk of venous thromboembolism due to hospitalization, immobilization, active infection and inflammation, and possibly due to a hypercoagulable state unique to the virus itself. Arterial thrombosis has also been reported.
- COVID-19 infected patients display multiple coagulation abnormalities which may be more prothrombotic than hemorrhagic
- Lab derangements may include elevated d-dimers, prolonged PT/PTT high fibrinogen and sometimes mild thrombocytopenia
- This document is based on expert clinical guidance and current best available information, which is still evolving. This guidance should be used in conjunction with latest evidence and patient-specific characteristics and should not supersede clinical judgment

ANTICOAGULATION ADMISSION CONSIDERATIONS FOR HIGHLY SUSPECTED OR CONFIRMED COVID

- Labs on admission: D-dimer, INR/PT, PTT, fibrinogen and CBC with differential
  - Elevated D-dimer is of unknown clinical significance and should not be used as a lone criterion in care decisions
- Inpatient labs every 2-3 days: CBC, PT, PTT, D-dimer, INR/PT, fibrinogen
  - If worsening parameters, consider more aggressive critical care support
  - Do not use blood products to correct non-bleeding coagulopathy
  - There is no evidence for use of TEG in COVID-19 patients to guide decisions regarding anticoagulation and use is NOT recommended

THERAPEUTIC ANTICOAGULATION PRIOR TO ADMISSION

- If a patient was receiving anticoagulation therapy prior to admission for a co-morbid disease state, continue anticoagulation therapy during COVID admission if no contraindications exist
  - Monitor renal function daily
- Consider switching to enoxaparin or heparin infusion if severe illness, possible drug-interactions with COVID investigational therapies, inability to take PO medications or anticipated procedures

PREVENTION OF VENOUS THROMBOEMBOLISM (VTE) IN HIGHLY SUSPECTED OR CONFIRMED COVID PATIENTS

- The American Society of Hematology (ASH) guideline suggests prophylactic-intensity over intermediate-intensity or therapeutic-intensity anticoagulation for patients with COVID-19–related illness who do not have suspected or confirmed venous thromboembolism (VTE)
- The International Society on Thrombosis and Haemostasis (ISTH) recommends routine thromboprophylaxis with standard-dose UFH or LMWH should be used after careful assessment of bleed risk, with LMWH as the preferred agent. VTE prophylaxis recommendations should be modified based on extremes of body weight, severe thrombocytopenia or deteriorating renal function.
• All highly-suspected or confirmed COVID-19 patients not on anticoagulation therapy should receive VTE prophylaxis unless contraindicated (e.g., Platelet count <25-30K, active bleeding) – see Figure 1.

• Low molecular weight heparin (enoxaparin), appropriately dose adjusted for renal function and/or weight is the preferred agent for thromboprophylaxis (see Figure 1)
  o Therapy adjustments are required for impaired renal function and/or extremes of weight (see Figure 1)
  o Fondaparinux may be used as an alternative to enoxaparin for patients with heparin induced thrombocytopenia without contraindications

• If pharmacologic prophylaxis is contraindicated, mechanical prophylaxis with intermittent pneumatic compression (IPC) should be consistently applied

• VTE prevention regimens and recommendations include pregnant COVID+ patients. Close collaboration with OB and anesthesiology is recommended in the event of delivery and/or need for epidural anesthesia during hospitalization.

**Figure 1: VTE Prophylaxis**

<table>
<thead>
<tr>
<th>VTE Prophylaxis for ALL Hospitalized Highly-Suspected or Confirmed COVID-19 Patients without Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl</td>
</tr>
<tr>
<td>BMI less than 40</td>
</tr>
<tr>
<td>40 QD</td>
</tr>
<tr>
<td>BMI 40 or greater</td>
</tr>
</tbody>
</table>
*For patients <50 kg and age >80 YO, dose adjustment to Heparin 5000 units SubQ q12 hour
If pharmacologic prophylaxis contraindicated (active bleeding, PLT <25K): SCDs*

**Monitoring:**
CrCl and CBC: Daily for critically ill, or every 2-3 days for other hospitalized
PTT, PT/INR, D-Dimer, fibrinogen: Every 2-3 days

**Empiric Therapeutic Anticoagulation for COVID Related Coagulopathy**

• Initiation of therapeutic anticoagulation regimens without confirmed or high clinical suspicion of VTE is not recommended at this time (see ASH and ISTH references).

• Suspected VTE should be confirmed with diagnostic imaging whenever feasible if patient is stable to do so.

• Severe COVID-19 infections may be associated with significant coagulopathy. Reported microvascular thrombosis is a distinctly different entity from embolic DVT/PE and when present in other inflammatory conditions such as sepsis, which does not respond to anticoagulant therapy and bleeding risk is high.

• Currently anticoagulants are not recommended to treat suspected microvascular thrombosis. In contrast, embolic VTE, responds to anticoagulant therapy.

• In the setting of persistent clotting of lines/devices/filters despite COVID-appropriate VTE prophylaxis and worsening clinical course, intensified anticoagulation may be considered via multidisciplinary discussion with critical care attending, coagulation specialist, or others (path, heme) where available.

**Empiric Thrombolytic Therapy**

• Empiric use of thrombolytic (i.e. alteplase) is NOT recommended for COVID-19 associated coagulopathy (outside of a clinical trial).

• Thrombolysis may be considered for COVID-19 patients with confirmed or high suspicion for indications specific to thrombolytic therapy (i.e., acute ischemic stroke, PE, acute myocardial infarction).

**Treatment of Venous Thromboembolism (VTE) in Highly Suspected or Confirmed COVID Patients**

• Suspected VTE should be confirmed with diagnostic imaging whenever feasible if patient is stable to do so.
• Initiate therapeutic anticoagulation (unless contraindicated) only when VTE is confirmed or clinical suspicion is high and diagnostic testing is unavailable or not feasible.

• Anticoagulation regimens that require minimal monitoring and RN exposure are preferred when possible (see Figure 2).

• The PTT may be impacted by the virus and thus not reliable in some COVID-19 patients. If available, recommend a correlation is performed between PTT/Anti-FXa at the time IV Unfractionated Heparin (UFH) is started and again if significant worsening of clinical status. Discuss with local laboratory.

• Limit treatment regimens for VTE in COVID+ pregnant patients to enoxaparin or UFH. DOACs are contraindicated in pregnancy and breastfeeding.

**Figure 2 : Therapeutic Anticoagulation for Treatment of VTE in COVID Patients**

<table>
<thead>
<tr>
<th>Preferred Treatment Regimens for Highly-suspected or Confirmed VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl</td>
</tr>
<tr>
<td>CrCl &gt; 30 ml/min</td>
</tr>
<tr>
<td>CrCl 29 - 10 ml/min</td>
</tr>
<tr>
<td>CrCl &lt; 10 ml/min</td>
</tr>
</tbody>
</table>

**Thromboprophylaxis and Anticoagulation Nursing Considerations**

- Goals of care include prevention of ischemic injury and dehydration, absence of hemorrhage and restoration of homeostatic coagulation. Collaborate with pharmacist and medical staff regarding appropriate anticoagulant dose.

- Management of care include:
  - Regular assessment for signs/symptoms of bleeding
    - Assess skin for hematoma or mottling; Monitor lab values; Assess capillary refill
    - Assess vital signs, watching for arrhythmias, tachycardia and hypotension
  - Assess neuro status
  - Keep venipuncture to a minimum

**Anticoagulation Discharge Considerations**

**Post Hospitalization Considerations for Patients Treated With Therapeutic Anticoagulation for Suspected or Confirmed VTE During COVID Admission**

- If acute VTE was confirmed during admission, continue therapeutic anticoagulation at least 3 months then re-assess.

- If VTE was unconfirmed & treated empirically for a patient with high suspicion, continue therapeutic anticoagulation for at least 3 months then re-assess.

**Post Hospitalization Considerations - VTE Prophylaxis**

- Severely ill COVID-19 patients may experience prolonged hospital stay, significant deconditioning, post-ICU syndrome and thus may not fully recover to baseline mobility or health status by time of discharge. Patients being discharged from the Emergency Department (ED) with confirmed COVID-19 diagnosis may also be at risk for VTE.

- While no data specific to COVID-19 exist, extended prophylaxis with LMWH or with direct oral anticoagulants (DOACs) in non-COVID-19 patients can reduce the risk of VTE, at the cost of increase in bleeding events, including major bleeding.

- Each COVID-19 patient should have a careful risk assessment on a case-by-case basis based on the presence ongoing risk factors for VTE at the time of discharge.

- VTE prophylaxis beyond discharge from the hospital, may be reasonable on a case-by-case basis and may include COVID-19+ patients who have:
  - Diminished mobility / weakness
  - Active cancer
  - An ongoing inflammatory state
• Patients considered to be at significant continued risk for VTE AND without elevated bleeding risk factors should be **considered** (no data exists) for:
  o Short-term use (up to 14 days) of prophylactic dose LMWH or DOAC (dose based on weight, renal function, and drug interaction screening\(^3\)).
• Prophylaxis dosing with enoxaparin or DOAC for up to 14 days and re-evaluation after beyond hospitalization may be reasonable in appropriately selected patients with reduced mobility and increased thrombotic risk factors
  o Patient education on the potential bleeding risk and expected benefit is required prior to prescribing post-discharge VTE prophylaxis.
• For those patients admitted for treatment of COVID-19 who may have been on thromboprophylaxis for conditions that existed prior to admission, consider transition back to the previous regimen (consider changes in renal function) post-hospitalization (if the pre-hospitalization condition still exists).
Clinical Suspicion for VTE

VTE unlikely (Wells score PE ≤ 4, DVT < 2)
Continue VTE prophylaxis with close monitoring for further signs and symptoms of VTE
Consider discharge on VTE prophylaxis for up to 14 days (see Discharge Considerations)

VTE likely (Wells Score PE >4, DVT ≥ 2)
Assess VTE-BLEED score

Low risk for bleeding (VTE-BLEED Score ≥ 2)
VTE treatment

High risk for bleeding (VTE-BLEED Score ≥ 2)
Consider PE CT or LE DVT scan as per clinical suspicion

COVID VTE protocol exclusion criteria
If yes to any of these criteria, no further studies should be performed. Otherwise, continue algorithm
- Patient is end of life or comfort care
- VTE imaging would not change management
- Patient would not consent to therapeutic anticoagulation
- Patient already has dx of VTE from another study or other indications for therapeutic anticoagulation

VTE (+) or presumptive

VTE (-)
Consider PE CT or LE DVT scan as per clinical suspicion
Continue current management
Consider VTE prophylaxis if not already on

a. See Figure 2. Enoxaparin preferred to IV UFH to minimize need for lab monitoring and RN exposure.
b. If imaging can’t be done but suspicion for VTE is high, may consider cautious use of presumptive therapeutic anticoagulation with close monitoring for bleeding
### Modified Wells Score for Assessment of Clinical Likelihood of VTE

*Not validated in COVID but no other score available*

<table>
<thead>
<tr>
<th>PE Criteria</th>
<th>Pt</th>
<th>DVT Criteria</th>
<th>Pt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs and symptoms of DVT (objectively measured calf swelling and pain with palpation in the deep vein region)</td>
<td>3</td>
<td>Active cancer (patient receiving treatment for cancer within the previous 6 months or currently receiving palliative treatment)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paralysis, paresis, or recent casting or immobilization of the lower extremities</td>
<td>1</td>
</tr>
<tr>
<td>An alternative diagnosis is less likely than PE</td>
<td>3</td>
<td>Recently bedridden for 3 days or more, or major surgery within the previous 12 weeks requiring general or regional anesthesia</td>
<td>1</td>
</tr>
<tr>
<td>Heart rate &gt; 100 beats per minute</td>
<td>1.5</td>
<td>Localized tenderness along the distribution of the deep venous system</td>
<td>1</td>
</tr>
<tr>
<td>Immobilization or surgery in the previous four weeks</td>
<td>1.5</td>
<td>Entire leg swollen</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Calf swelling at least 3 cm larger than that on the asymptomatic side (measured 10 cm below the tibial tuberosity)</td>
<td>1</td>
</tr>
<tr>
<td>Previous DVT or PE</td>
<td>1.5</td>
<td>Pitting edema confined to the symptomatic leg</td>
<td>1</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1</td>
<td>Previously documented DVT</td>
<td>1</td>
</tr>
<tr>
<td>Malignancy (on treatment, treated in the past six months, or palliative care)</td>
<td>1</td>
<td>Collateral non-varicose superficial veins</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alternative diagnosis at least as clinically likely as DVT</td>
<td>-2</td>
</tr>
<tr>
<td>OR acute change in O2 req</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### VTE-BLEED Score

<table>
<thead>
<tr>
<th>Factor</th>
<th>Score</th>
<th>Other factors that contribute to bleeding:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer</td>
<td>2</td>
<td>• Thrombocytopenia</td>
</tr>
<tr>
<td>Male with uncontrolled arterial hypertension</td>
<td>1</td>
<td>• Cirrhosis</td>
</tr>
<tr>
<td>Anemia</td>
<td>1</td>
<td>• Other anti-thrombotic use (e.g. aspirin, clopidogrel, ticagrelor)</td>
</tr>
<tr>
<td>History of bleeding</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Age ≥ 60 years old</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

### Anticoagulation References:


REFERENCES:


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**VERSION HISTORY**

<table>
<thead>
<tr>
<th>Version Date</th>
<th>Revisions Made</th>
</tr>
</thead>
<tbody>
<tr>
<td>3/30/2020</td>
<td>Updated Remdesivir compassionate use information.</td>
</tr>
<tr>
<td>4/4/2020</td>
<td>Updated to reflect new FDA released FACT SHEET FOR HEALTH CARE PROVIDERS and expanded information in 'Use of Hydroxychloroquine: Patient Selection, Dosing, and Monitoring&quot; section</td>
</tr>
<tr>
<td>Date</td>
<td>Changes</td>
</tr>
<tr>
<td>------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>4/28/2020</td>
<td>Added reference to FDA Drug Safety Communication that cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems. Added information on Discharging Patients on Hydroxychloroquine</td>
</tr>
<tr>
<td>05/4/2020</td>
<td>Added outpatient pharmacotherapy guidance.</td>
</tr>
<tr>
<td>05/6/2020</td>
<td>Updated patient categories and therapy guidance for Remdesivir and Hydroxychloroquine. Includes updates for Remdesivir based on FDA emergency use authorization for Remdesivir.</td>
</tr>
<tr>
<td>05/13/2020</td>
<td>Recommendation added to limit use of triple antiviral therapy and interferon beta to use in a clinical trial only</td>
</tr>
<tr>
<td>5/20/2020</td>
<td>Updated recommendations on use of Remdesivir in renal impairment and duration of therapy. Nursing considerations comment added.</td>
</tr>
<tr>
<td>5/28/2020</td>
<td>Hydroxychloroquine no longer recommended</td>
</tr>
<tr>
<td>6/4/2020</td>
<td>Revised criteria for use of IL-6 inhibitors</td>
</tr>
<tr>
<td>6/16/2020</td>
<td>Information regarding FDA revocation of emergency approval of Hydroxychloroquine added. Remdesivir information updated with revised warnings for drug interactions and hypersensitivity and anaphylactic reactions.</td>
</tr>
<tr>
<td>6/24/2020</td>
<td>Addition of recommendation for dexamethasone/corticosteroid therapy for patients requiring oxygen therapy</td>
</tr>
<tr>
<td>7/13/2020</td>
<td>Convalescent Plasma guidance is updated and added to guidance document. Updated IL-6 section with results of sarilumab trial. NMBA guidance incorporated into the document. Addition of recommendation for glucose monitoring with corticosteroid use.</td>
</tr>
<tr>
<td>8/27/2020</td>
<td>Removal of option to extend Remdesivir duration from the recommended 5 day to a 10-day duration.</td>
</tr>
<tr>
<td>9/14/2020</td>
<td>Information added on new FDA EUA for convalescent plasma. Remdesivir EUA information updated to reflect the expansion of EUA to all hospitalized patients. Updated IL-6 information; routine use of IL-6 agents is not recommended based on new data. Co-infection (bacterial and influenza) recommendations added.</td>
</tr>
<tr>
<td>9/22/2020</td>
<td>Remdesivir treatment for suspected or confirmed non-severe disease updated &quot;Remdesivir is recommended for hospitalized patients not requiring supplemental oxygen with clinical symptoms of COVID-19 and a positive molecular (PCR) test&quot;</td>
</tr>
<tr>
<td>10/6/2020</td>
<td>Corticosteroid guidance updated with IDSA recommendations.</td>
</tr>
<tr>
<td>10/27/2020</td>
<td>Remdesivir EUA information for adults removed; Remdesivir FDA approved package insert information and updated monitoring (including addition of PT to daily labs) added. Updated influenza co-infection information to include empiric oseltamivir use pending testing results.</td>
</tr>
<tr>
<td>11/23/2020</td>
<td>Clarification that patients deemed stable for discharges should not be held in the hospital to complete a 5-day course of Remdesivir. Addition of monoclonal antibody EUA approval information. Addition of JAK inhibitor/Baricitinib EAU information.</td>
</tr>
<tr>
<td>12/3/2020</td>
<td>Update to Convalescent plasma recommendation and associated new publications.</td>
</tr>
<tr>
<td>12/10/2020</td>
<td>Update to Remdesivir recommendations and associated new publications.</td>
</tr>
<tr>
<td>1/26/2021</td>
<td>Update to IL-6 Inhibitor recommendation and associated new publications. Addition of Ivermectin recommendation.</td>
</tr>
<tr>
<td>2/18/2021</td>
<td>Update of Bamlanivimab administration information and addition of Bamlanivimab and Etesevimab to monoclonal antibody options. Revision of IL6 recommendation.</td>
</tr>
<tr>
<td>3/19/21</td>
<td>Update of Monoclonal Antibody section to provide guidance on impact of variants on product selection.</td>
</tr>
<tr>
<td>4/30/21</td>
<td>Update to Convalescent Plasma guidance to consider use of high-titer only for patients with impaired immunity.</td>
</tr>
<tr>
<td>Date</td>
<td>Update</td>
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<tr>
<td>5/25/21</td>
<td>Update to definition of high risk for disease progression for monoclonal antibody therapy</td>
</tr>
<tr>
<td>6/9/21</td>
<td>Updated Casirivimab and Imdevimab (REGEN-COV™) dose and route options. Updated recommendation for Immunomodulators in severe disease: either Tocilizumab or Baricitinib in addition to corticosteroids for patients not requiring mechanical ventilation.</td>
</tr>
<tr>
<td>8/9/21</td>
<td>Updated Casiririmab and Imdevimab links to the revised Emergency Use Authorization (EUA) and Fact Sheets. Inserted link to new guidance for Casiririmab and Imdevimab use for post-exposure prophylaxis. Updated Baricitinib guidance to reflect new EUA that authorizing use as a stand alone treatment instead of only in combination with Remdesivir</td>
</tr>
<tr>
<td>9/7/21</td>
<td>Removed Convalescent Plasma from recommendations; updated Bamlanivimab and Etesevimab recommendation to include use for areas approved by the FDA where the combined frequency of variants resistance does not exceed 5%; Added IV Sarilumab as an alternative IL-6 inhibitor if tociluzimab is not available, and tofacitinib as an alternative JAK inhibitor if baricitinib is unavailable; Revised VTE prophylaxis recommendations for use of standard prophylaxis dose instead of moderate dose</td>
</tr>
<tr>
<td>9/24/21</td>
<td>Updated to reflect EUA changes for Bamlanivimab and Etesevimab prophylactic use post high risk exposure.</td>
</tr>
<tr>
<td>12/03/2021</td>
<td>Update includes guidance for pregnant patients being treated for COVID</td>
</tr>
<tr>
<td>12/03/2021</td>
<td>Addition of PAXLOVID and Molnupirivir</td>
</tr>
<tr>
<td>01/11/2022</td>
<td>Addition of Remdesivir for outpatient treatment of mild to moderate disease.</td>
</tr>
</tbody>
</table>