Clinical Recommendations for Evaluation and Management of COVID-19 Adult Patients

Written by: VUMC Faculty in Anesthesiology, Cardiology, Emergency Medicine, Hematology, Hospital Medicine, Infectious Diseases, Internal Medicine, Pharmacy, Pulmonary/Critical Care, & Radiology

Approved by: VUMC Adult Clinical Practice Committee

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Summary

This document highlights key updates to VUMC's COVID-19 evaluation and management guidelines as of **May 27, 2022**. Updates to previously released guidance appear in red below. Please consult the VUMC Coronavirus (COVID-19) Information website for additional information.

This document was developed after review of organizational guidelines [e.g., National Institutes of Health (NIH), Infectious Diseases Society of America (IDSA)] and peer-reviewed literature. Group consensus from a multidisciplinary group of experts was obtained, and the Adult Clinical Practice Committee has reviewed and approved prior to dissemination.

Inpatient Care

1. General Guidelines for Admitted Patients with Symptomatic Acute COVID-19 Infection

- Admission criteria for COVID-19 are identical to those for other viral pneumonias (i.e., influenza).
- Patients who are diagnosed with COVID-19 based on screening for other purposes (i.e., admission, pre-surgical screening) may not require further evaluation. Additional diagnostic testing should be based on the medical provider's assessment and discretion.
- Testing for patients to be admitted for suspected or confirmed COVID-19:
    - All patients with symptomatic suspected or confirmed COVID-19 should receive the following diagnostic testing: CBC with differential, CMP, respiratory pathogen panel (RPP)*, and Chest X-ray.
        - *Note that RPP testing cannot be "added on" to a swab already in the lab. If RPP testing is needed, it should be ordered at the same time as the SARS-CoV-2 PCR. If RPP testing is needed after the SARS-CoV-2 PCR is resulted, then a new sample must be sent to the lab.
    - For patients with confirmed COVID-19, obtain baseline D-dimer quant, ferritin level, CRP, ESR, PT/INR, PTT, and procalcitonin testing for management and prognostic indications.
        - Note that elevated D-dimer is a poor prognostic indicator for COVID-19 but alone does not indicate need for DVT/PE evaluation.
        - Troponin and BNP should not be routinely measured in the absence of other evidence of MI or CHF.
    - Daily laboratory testing is NOT recommended for patients who are clinically improving or in patients where testing is not expected to change management.
    - For efficiency in patient care and for mitigation of potential exposure to patients and staff, portable AP Chest X-rays are preferred.
    - Chest CT is NOT recommended in COVID-19 screening and initial diagnosis.
        - There is no indication for Chest CT in symptomatic COVID-19 patients who are well enough to be sent home from the ED or outpatient setting.
        - Chest CT may be helpful in assessing suspected complications of hospitalized COVID-19 inpatients, including abscess or empyema.
        - Chest PE studies should be limited to symptomatic COVID-19 patients with sudden or rapid worsening of hypoxia or new onset chest pain that is not cardiac in origin.
- Telemetry is not routinely indicated in COVID-19 patients unless the patient meets other criteria.
- Restrictive fluid management is recommended to avoid pulmonary edema. Order strict intake and output on admission. Attempt to keep an even fluid balance.
- Antibiotics for pneumonia (e.g., ceftriaxone and azithromycin or levofloxacin) may be considered in suspect COVID-19 patients with chest imaging consistent with pneumonia pending results of COVID-19 testing and RPP.
- A "COVID-19 Accordion Report" is available in eStar to assist with patient care. The report includes common labs, administered antibiotics/antivirals/corticosteroids, and links to chest imaging and culture reports. The COVID-19 Accordion Report is available from the Patient List or from the Summary tab within a patient's eStar chart.

- Decision to transfer to higher level of care (ICU) should be made using current level-of-care standard operating procedures (SOPs) in conjunction with either an ICU provider and/or rapid response team.
- Patients requiring ≤ 80% FiO2 via Optiflow for ≥ 72 hours in the ICU may be considered for stepdown transfer.
- Discharge criteria for COVID-19 are similar to those for other viral pneumonias, and a patient does not have to be afebrile at the time of discharge.
    - Patients who test positive for COVID-19 and are being discharged after hospitalization for COVID-19 infection should self-isolate x 20 days after the test was obtained AND until improving and fever-free x 24 hours. This is recommended even if patients have been previously vaccinated.
    - For patients who require SNF placement at discharge, discuss individual needs and discharge requirements with VUMC case management.

2. Recommendations for Remdesivir in Symptomatic Hospitalized COVID-19 Patients

- For hospitalized patients, remdesivir may be considered, as approved by the Food and Drug Administration (FDA). Based on the NIH COVID-19 Treatment Guidelines, patients being considered for remdesivir at VUMC should meet all the following criteria:
        - Hospitalized with confirmed positive SARS-CoV-2 PCR
        - ≤7 days since onset of symptoms
        - Absence of all the following:
            - Known hypersensitivity to remdesivir
            - ALT $\geq$ 10 times the upper limit of normal
            - NOTE: Remdesivir is not recommended in patients with eGFR <30 ml/min per the FDA package insert. After review of the available data and consultation with nephrology at VUMC, we allow use of remdesivir in patients with eGFR <30 ml/min at the discretion of the treating clinicians
            - Requires Optiflow, non-invasive ventilation, mechanical ventilation, or ECMO
    - Dose:
        - For patients who require supplemental oxygen but do not require Optiflow, non-invasive ventilation, mechanical ventilation, or ECMO:
            - Loading dose 200 mg IV x 1 then 100 mg IV q24h x 4 days (for a total of 5 days of therapy)
                - NOTE: Patients who are ready for discharge should not remain hospitalized solely to complete the full course of remdesivir.
                - NOTE: Remdesivir may be discontinued in patients who initially require supplemental oxygen but then progress to Optiflow, non-invasive ventilation, mechanical ventilation, or ECMO support.
        - **For patients admitted for other indications but who are found to have mild-to-moderate symptomatic COVID-19 and are at high risk of progression to severe COVID-19 disease, remdesivir IV x 3 days may be used as an alternative to monoclonal antibody treatment. This is preferred when monoclonal antibody supply is limited.**
            - **Loading dose 200 mg IV x 1 then 100 mg IV q24h x 2 days (for a total of 3 days of therapy)**
                - **NOTE: Patients who are ready for discharge should not remain hospitalized solely to complete the full course of remdesivir, though this may be considered as part of discharge planning.**
                - **NOTE: Remdesivir may be extended to 5 days in patients who progress to severe COVID-19 disease.**
                - **NOTE: Remdesivir may be discontinued in patients who progress to requiring Optiflow, non-invasive ventilation, mechanical ventilation, or ECMO support.**

- Monitoring:
  - CBC at baseline and as needed
  - CMP at baseline and every other day
  - PT/INR at baseline and as needed
  - Monitor patients during infusion and observe patients for at least one hour after infusion is complete for signs and symptoms of hypersensitivity as clinically appropriate.
- Adverse Effects and Precautions:
  - Infusion related reactions
  - Transaminase elevations
  - PT prolongation
  - Due to concerns for drug interactions, hydroxychloroquine used for rheumatologic disorders should be held while patients are receiving remdesivir.
  - Symptomatic bradycardia has been observed rarely. Should symptomatic bradycardia occur, remdesivir should be discontinued.
- Restrictions, Approvals, and Ordering:
  - Remdesivir is FDA approved for the treatment of COVID-19.
  - Remdesivir is not restricted to specific providers and does not require specialty consultation for approval.

NOTE: *Combined use of nirmatrelvir/ritonavir, molnupiravir, and/or remdesivir is NOT currently recommended.*

3. Recommendations for Corticosteroids in Hospitalized COVID-19 Patients

- For hospitalized patients with COVID-19 who require supplemental respiratory support (including supplemental oxygen, non-invasive ventilation, mechanical ventilation, or ECMO), ***treat with dexamethasone 6 mg PO daily for 10 days***, unless contraindicated. Dexamethasone 6 mg daily may be given IV if the patient is unable to tolerate PO medications.
- **Some evidence suggests that a higher dose of dexamethasone (12 mg) may reduce mortality in patients with severe COVID-19 on >= 10L/min oxygen who are not eligible for or cannot access other treatments (e.g., baricitinib, tocilizumab). (https://jamanetwork.com/journals/jama/fullarticle/2785529) Dexamethasone 12 mg daily may be considered in patients with severe COVID-19 requiring >=10L/min who are clinically worsening despite 6 mg daily and who are not eligible or cannot access alternative treatments. Some data suggest higher doses of dexamethasone may be detrimental in patients on no oxygen or low flow oxygen.**
- Other corticosteroids may be considered in hospitalized patients with COVID-19 who require supplemental respiratory support and cannot be treated with dexamethasone. In accordance with NIH recommendations, if dexamethasone is not available, prednisone 40 mg PO daily OR methylprednisolone 32 mg PO daily OR hydrocortisone 50 mg IV q8h may be used as an alternative to dexamethasone.
- For pregnant hospitalized patients with COVID-19 who require supplemental respiratory support (including supplemental oxygen, non-invasive ventilation, mechanical ventilation, or ECMO), dexamethasone or methylprednisolone should be administered given the potential benefit of decreased maternal mortality and the low risk of fetal adverse effects for short course glucocorticoid therapy.
- Inpatients who are ready for discharge in stable condition but require supplemental oxygen prior to completion of the course of dexamethasone should be given a prescription to complete the 10-day course of steroids after discharge unless otherwise contraindicated. Inpatients who are ready for discharge in stable condition and do not require supplemental oxygen at discharge may not require completion of a course of dexamethasone.
- Immunosuppression, including glucocorticoid use, may increase the risk of hyperglycemia, as well as serious infection from bacteria, fungi, and parasites.
- **Given the very limited data on continuing steroids beyond the initial 10-day course in patients who are worsening or still have markedly elevated inflammatory markers, the decision to extend treatment should be made by the treating provider on a case-by-case basis.**

4. Recommendations for Baricitinib in Hospitalized COVID-19 Patients

- Baricitinib may be considered as an adjunctive therapy for hospitalized patients with symptomatic COVID-19 infection. Baricitinib may also be used at VUMC in patients who are unable to tolerate or have contraindications to corticosteroids.
- Patients being considered for baricitinib at VUMC should meet all the following criteria:
    - If used in conjunction with corticosteroids:
        - Hospitalized with confirmed positive SARS-CoV-2 PCR
        - Requiring ≥6 L/min via nasal cannula or >40% FiO2
        - ≤7 days since admission to the hospital
        - Clinically worsening despite corticosteroid therapy (e.g., dexamethasone) and supportive care
    - If used in place of corticosteroids:
        - Hospitalized with confirmed positive SARS-CoV-2 PCR
        - Requires supplemental oxygen
        - Recently received or receiving antiviral therapy (e.g., remdesivir, nirmatrelvir/ritonavir, or molnupiravir)
    - Absence of all the following contraindications to baricitinib:
        - Hypersensitivity to baricitinib
        - Concurrent treatment with tocilizumab
        - Dialysis, end-stage renal disease (eGFR <15 ml/min), or acute oliguric/anuric kidney injury
        - Severe hepatic impairment, defined as ALT ≥ 10 times the upper limit of normal
        - Known active tuberculosis or systemic fungal infection
        - Pregnancy
    - Dose:
        - In patients taking a strong Organic Anion Transporter 3 (OAT3) inhibitor (e.g., probenecid), the dose of baricitinib should be reduced by 50%; for patients with eGFR 15-29 ml/min and on probenecid, consider discontinuing the probenecid.
        - For patients with **eGFR ≥ 60 ml/min**, baricitinib 4 mg po once daily for 14 days in total or until hospital discharge.
        - For patients with **eGFR 30-59 ml/min**, baricitinib 2 mg po once daily for 14 days in total or until hospital discharge.
        - For patients with **eGFR 15-29 ml/min**, baricitinib 1 mg po once daily for 14 days in total or until hospital discharge.
    - Monitoring:
        - CBC with diff and CMP at baseline
    - Adverse Effects and Precautions:
        - Thrombosis, including pulmonary embolism
            - Baricitinib has a black box warning for thrombotic events.
            - As hospitalized patients with COVID-19 may be at increased risk for thrombosis, patients with COVID-19 on baricitinib should be closely monitored for signs or symptoms of thrombosis.
            - The benefits and risks of continuing baricitinib in a patient with COVID-19 and newly discovered thrombosis are unknown. Providers should consider the patient, clinical context, and current treatment plan when deciding whether to continue baricitinib, discontinue baricitinib, or replace baricitinib with an alternative agent.
        - Severe infection
        - Transaminase elevations
        - Lymphopenia
        - Neutropenia

- Restrictions, Approvals, and Ordering:
    - Baricitinib eligibility and approval may be discussed with the patient's ID, Pulmonary/CCM, or Rheumatology consultants.

5. Recommendations for Tocilizumab in Hospitalized COVID-19 Patients

- Tocilizumab may be considered as an adjunctive therapy for hospitalized patients with symptomatic COVID-19 infection.
- Based on current guidelines, this medication should be used only in patients who meet criteria and who are not eligible for baricitinib.
- Patients being considered for tocilizumab at VUMC should meet all the following criteria:
    - Hospitalized with confirmed positive SARS-CoV-2 PCR
    - Requiring ≥6 L/min via nasal cannula or >40% FiO2
    - ≤7 days since admission to the hospital
    - Clinically worsening despite corticosteroid therapy and supportive care
    - Contraindication to baricitinib
    - Absence of all the following contraindications to tocilizumab:
        - Hypersensitivity to tocilizumab
        - Concurrent treatment with baricitinib
        - Recent history of diverticulitis
        - History of bowel perforation
        - Demyelinating disorders, such as multiple sclerosis
        - ALT $\geq$ 5 times the upper limit of normal
        - Absolute neutrophil count <500 cells/µL
        - Platelet count <50,000 cells/µL
        - Active infection with bacterial (including tuberculosis), fungal, or acute viral infection other than COVID-19
            - NOTE: Patients with HIV or chronic viral hepatitis may be considered for treatment.
- Dose:
    - 8 mg/kg, up to maximum of 800 mg, IV once
        - NOTE*:* Based on currently available data, a second dose of tocilizumab for the treatment of patients with COVID-19 is not recommended at VUMC.
- Monitoring:
    - No specific laboratory monitoring recommended
- Adverse Effects and Precautions:
    - Infusion related reactions
    - Serious infections
    - Gastrointestinal perforations
    - Liver enzyme abnormalities
    - Elevated lipids while on therapy
- Restrictions, Approvals, and Ordering:
    - Tocilizumab eligibility and approval may be discussed with the patient's ID, Pulmonary/CCM, or Rheumatology consultants.
    - The EUA Fact Sheet should be provided to the patient and/or caregiver and documentation that it was reviewed should be placed in the clinical record.
    - Medication errors and/or serious adverse events believed to be related to tocilizumab administration should be reported to the VUMC Pharmacy, who will assist with submitting the required FDA MedWatch reports within 7 days of event.

6. Recommendations for Monoclonal Antibody Treatment in Hospitalized COVID-19 Patients

- For patients ≥12 years old and at least 40 kg with symptomatic COVID-19 (e.g., respiratory symptoms not requiring supplemental oxygen, cough, anosmia, change of taste, gastrointestinal symptoms), monoclonal antibody treatment has been authorized through an Emergency Use Authorization by the Food and Drug Administration (FDA) for treatment of COVID-19 infected patients.
- **Monoclonal antibodies are approved for treatment of mild to moderate COVID-19 in patients at risk for progression to severe disease. Due to variable activity against circulating strains and limited supply, patients hospitalized for other indications but who are found to have mild-to-moderate COVID-19 should preferentially be treated with remdesivir.**

7. Recommendations for Antibiotics in Hospitalized COVID-19 Patients

- If COVID-19 testing is positive and the serum procalcitonin value is <0.25 µg/L, stopping antibiotics (if previously started) is strongly encouraged unless clear concern for or evidence of a secondary bacterial infection.
- If COVID-19 testing is positive and the serum procalcitonin value is 0.25-0.5 µg/L, stopping antibiotics (if previously started) is encouraged unless clear concern for or evidence of a secondary bacterial infection.
- If COVID-19 testing is positive and the serum procalcitonin value is >0.5 µg/L, consider beginning or continuing antibiotics (if previously started) and pursuing additional work up for secondary bacterial infection, if the patient is not requiring ICU-level care.
- NOTE: Procalcitonin may be elevated in severe COVID-19 infection without concomitant bacterial infection.

8. Recommendations for VTE Prophylaxis in Hospitalized COVID-19 Patients

- Patients admitted for COVID-19 with non-critical illness requiring supplemental oxygen by nasal cannula and/or a venti-mask/non-rebreather mask benefit from therapeutic dose anticoagulation, unless contraindicated.
- Patients admitted for another diagnosis who are found to be positive for COVID-19 should receive standard VTE pharmacologic prophylaxis, as designated by the DVT prophylaxis advisor, unless contraindicated. These patients may be asymptomatic or mildly symptomatic (e.g., respiratory symptoms not requiring supplemental oxygen, cough, anosmia, change of taste, gastrointestinal symptoms), and would NOT have been admitted for COVID-19 infection alone.
- Patients admitted for COVID-19 with critical illness requiring Optiflow, non-invasive ventilation, mechanical ventilation, and/or cardiovascular support do NOT benefit from therapeutic anticoagulation but should receive prophylactic anticoagulation based on the DVT prophylaxis advisor, unless contraindicated.
- Patients admitted for symptomatic COVID-19 who receive therapeutic anticoagulation but develop critical illness requiring Optiflow, non-invasive ventilation, mechanical ventilation, and/or cardiovascular support may continue therapeutic dosing, may receive prophylactic dosing, or discontinue prophylaxis based on the clinical context and the judgement of the treating provider. Upon transfer to routine floor or stepdown status, such patients should continue their current anticoagulant dose. If they remain on therapeutic dose anticoagulation for COVID-19, see guidance for duration below.
- Patients admitted for symptomatic COVID-19 with contraindications to therapeutic anticoagulation should be given prophylactic anticoagulation based on the DVT prophylaxis advisor, unless contraindicated.
- For patients with symptomatic COVID-19 who are on chronic anticoagulation with warfarin or DOACs at the time of admission, consider transitioning to therapeutic doses of enoxaparin or heparin IV (using the anti-Xa heparin protocol) with individualization based on medical condition.
- Recommended regimens for COVID-19 VTE prophylaxis with therapeutic doses include:
    - 1st Choice: enoxaparin 1 mg/kg twice daily
    - 2nd Choice: heparin IV, using the anti-Xa protocol

    - History of HIT: consult hematology
- Contraindications to therapeutic anticoagulation:
    - Active bleeding
    - Current use of dual antiplatelet therapy
    - Risk factors for bleeding, including:
        - Intracranial surgery or stroke within 3 months
        - History of intracerebral arteriovenous malformation
        - Cerebral aneurysm or mass lesions of the central nervous system
        - Intracranial malignancy
        - History of intracranial bleeding
        - History of bleeding diatheses (e.g., hemophilia)
        - History of gastrointestinal bleeding within previous 3 months
        - History of thrombolysis within the previous 7 days
        - Presence of an epidural or spinal catheter
        - Recent major surgery <14 days prior
        - Uncontrolled hypertension (SBP >200 mmHg, DBP >120 mmHg)
        - Platelet count <50,000 cells/µL
        - INR >2.0
        - Baseline aPTT >50 seconds
        - Acute or subacute bacterial endocarditis
        - Pregnancy in the third trimester (*Please consult benign hematology for further evaluation and recommendations)

- Duration of therapeutic dose anticoagulation for VTE prophylaxis
    - Therapeutic anticoagulation should be prescribed for 14 days, until hospital discharge, or liberation from the need for supplemental oxygen, whichever comes first.
    - If a patient remains admitted after completing 14 days of therapeutic anticoagulation, the patient should receive VTE pharmacologic prophylaxis as designated by the DVT prophylaxis advisor.

Perioperative VTE Prophylaxis in COVID-19 Positive Patients

- For all patients admitted for a procedure or surgery on an elective basis, routine prophylactic anticoagulation should be applied throughout the perioperative period.
- For patients admitted with an urgent or emergent procedure or surgery, anticoagulation should be applied as per the requirements of the procedure.
- For perioperative patients who are admitted with a new oxygen requirement, or who develop an oxygen requirement of ≥4L by nasal cannula, consultation with hematology for anticoagulation may be appropriate.

Patients Meeting Clinical Criteria for High Acuity COVID Follow-up:

- Patients discharged from the hospital or ED with high acuity follow up should be considered for VTE prophylaxis .
- Patients who are on therapeutic anticoagulation during hospitalization for COVID-19 should be transitioned to VTE prophylaxis upon transition to home.
- The preferred regimen is apixaban 2.5 mg PO Q12 hours.
    - Rivaroxaban 10 mg PO daily and enoxaparin 40 mg subcutaneous Q24hrs are alternatives. (NOTE: Enoxaparin dose adjustments are needed for patients at the extremes of weight.)
- Exclusion criteria for use of apixaban, rivaroxaban, or enoxaparin:
    - CrCl < 30 ml/min
    - Platelet count < 50,000 cells/µL
    - Severe liver disease with INR > 1.5
    - Known bleeding disorder (like hemophilia or von Willebrand disease)
    - Recent serious bleeding within 3 months (such as intracranial or GI bleeding)
    - High risk for bleeding, such as intracranial aneurysm/vascular malformation
    - High risk of falls
- Patients who are unable to take apixaban, rivaroxaban, or enoxaparin should be prescribed for aspirin 81 mg PO daily if not contraindicated.

- Patients should be prescribed a 7-day supply at hospital discharge. Please include “COVID-19 2 Home” in the prescription comments and consider using the VUMC pharmacy Meds to Beds to ensure patient has medication at the time of discharge.
- If patients meet clinical criteria for High Intensity C2H but are outside of the geographic catchment area, they may also be considered for 7-day VTE prophylaxis as above.

9. Recommendations for VTE Treatment in Hospitalized COVID-19 Patients

- For COVID-19 patients with a confirmed diagnosis of VTE (DVT or PE), enoxaparin 1 mg/kg BID is recommended, if not otherwise contraindicated.
    - Heparin IV (if not otherwise contraindicated) should be considered as an alternative for treatment of VTE in COVID-19 patients and should be dosed using the Anti-Xa Heparin protocol with individualization based on medical conditions.
    - If the patient is treated for proven DVT or PE, continue anticoagulation for 3 months or as per usual care.
    - NOTE: Enoxaparin may require dosing adjustments for renal impairment.
- For COVID-19 patients with a high suspicion of PE, consider empiric therapeutic anticoagulation as above.
    - If radiologic testing for PE is negative, but clinical suspicion remains high, consider consulting vascular medicine or benign hematology.
- For COVID-19 patients with a high suspicion of DVT, proceed with Doppler ultrasound and treat with therapeutic anticoagulation if DVT confirmed (including lower extremity DVT located above or below the knee).

10. Repeat COVID-19 PCR Testing in Symptomatic Inpatients

- Repeat testing of patients hospitalized with possible COVID-19 (i.e., compatible symptoms but had initial negative test result) should be reserved for patients for whom the clinician has a high index of suspicion AND a negative respiratory pathogen panel (RPP) AND a lack of alternative diagnosis.
- Checking additional COVID-19 tests for an inpatient who has already had two negative tests is not recommended, unless the patient clearly develops new symptoms which may indicate a *newly acquired* COVID-19 infection.
- Contact infection prevention if there are questions about continuing inpatient isolation after a negative COVID-19 test result.

11. Guidance on Management of Suspected Multisystem Inflammatory Syndrome in Adults (MIS-A) Following COVID-19

- Inflammatory conditions after COVID-19 infection have been well described in children, and cases have been increasingly identified in adults.
- MIS-A has been described approximately 2-8 weeks following previous COVID-19 diagnosis or known/suspected COVID-19 exposure, though not all patients will have had prior symptoms or have a known exposure.
- The CDC case definition for MIS-A is available at https://www.cdc.gov/mis/mis-a/hcp.html.
- Consider MIS-A in patients with fever without alternative etiology as well as clinical and/or laboratory evidence of organ dysfunction, including:
    - Cardiovascular manifestations: chest pain, arrhythmias, elevated troponin in the absence of acute coronary syndrome, elevated brain natriuretic peptide, reduced ejection fraction on transthoracic echocardiogram, and/or shock requiring vasopressor support
    - Hematologic manifestations: lymphopenia, thrombocytopenia, and/or relative decrease in platelet count associated with laboratory evidence of hyperinflammation (i.e., neutrophil predominant leukocytosis, ESR ≥ 50-100 mm/hour, CRP ≥ 150-200 mg/L, and/or ferritin ≥ 500-1000 ng/mL)
    - Gastrointestinal manifestations: abdominal pain, diarrhea, elevated liver function tests and hepatic dysfunction
    - Neurologic manifestations: altered mental status, meningitis, encephalopathy, and/or seizures

    - Skin and mucosa manifestations: Non-exudative conjunctivitis, mucositis, unilateral cervical adenopathy, edema of hands and/or feet, and rash (i.e., syndrome similar to Kawasaki syndrome in children)
- For further information regarding diagnosis and management, see COVID-19 Guidance for MIS-A.
- If treatment for MIS-A is indicated, strongly consider Rheumatology consultation for treatment recommendations and follow-up management.

12. Recommendations for Transfer or Discharge of Patients with COVID-19

- Some inpatients may be eligible for transfer to Hospital at Home. Hospital at Home is an innovative program that delivers hospital level care in the comfort of the patient's own home. Patients appropriate for Hospital at Home meet inpatient criteria and are felt to be clinically stable to complete their hospitalization at home. The program offers remote patient monitoring, daily in-person provider visits and twice daily in-person nursing visits. Referrals to HAH can be made by placing an Inpatient Consult to Hospital at Home order in eStar. The program can accept new patients from 7am to 3pm daily. Please contact the Oates MD attending with any questions regarding patient eligibility.
- Refer a patient to Hospital at Home by ordering "Inpatient Consult to Hospital at Home" in EStar.
  Hospital at Home admission criteria:
    - Inclusion:
        - Continues to meet inpatient criteria (if no longer requires hospitalization, please refer to COVID to Home)
        - Oxygenation stable/improving on ≤4L of supplemental O2 at rest AND with exertion
        - Presence of caregiver 24/7
    - Exclusion:
        - Increase in O2 requirement by >2L in the past 24 hours
        - 4C mortality score for COVID-19 ≥9
        - Signs of impending critical care requirement (e.g., severe dyspnea, increased work of breathing, cyanosis, inability to speak in full sentences, hemoptysis, chest pain/pressure not associated with coughing, altered mental status)
        - Symptoms/signs of COVID-19 cardiac pathologies (e.g., myocarditis, ACS, arrhythmia), or neurologic complications (e.g., delirium)
- **Isolation and Disposition:**
    - Patients who were hospitalized for COVID-19 infection should self-isolate x 20 days after the test was obtained AND until improving and fever-free x 24 hours.
    - If discharge to a post-acute care facility is anticipated, discuss with the primary team's case manager regarding COVID-19-specific requirements.
    - Patients may be seen in-person at any VUMC clinic after they have completed the required period of self-isolation. Patients should be instructed to wear a surgical mask if they continue to have respiratory symptoms at the time of their appointment.
- **Follow-up:**
    - Most patients do NOT need follow-up COVID-19 testing after a positive result. Exceptions may include patients requiring immune suppression or other medical interventions.
    - Follow up of discharged patients with COVID-19 should be arranged by the primary team and case management at the time of discharge.
    - For patients hospitalized with COVID-19, at the time of discharge, patients are eligible for post-discharge follow-up care:
        - **COVID High Acuity Follow-Up:**
            - **Consider a referral to home health for patients who are felt to be higher risk of decompensation or have had a higher acuity illness based on the following:**
                - **Hypoxia requiring new or increased home oxygen requirement**
                - **Patients who required ICU level care at any point during hospitalization with ongoing high symptom burden at time of discharge**
                - **Patients with significant comorbidities, particularly age 65 years or older, severe obesity, underlying heart or lung disease, who are**

within one year of organ transplantation or are severely immunocompromised

- **For patients referred to receive home health services from Vanderbilt Home Care, the team will arrange clinician visits with Vanderbilt Health OnCall when clinically indicated**
  - **Discharging clinicians should place a nurse order in eStar to supply the patient with a pulse oximeter as part of the discharge orders.**
  - **If there are any questions about the appropriate level of care needed or any unique care needs, please instruct case management to contact Vanderbilt Home Care Services at 615-835-5454.**
  - **Patients being discharged with high acuity follow up should be prescribed VTE prophylaxis at the discretion of the discharging provider as noted in above. Providers may choose not to prescribe VTE prophylaxis for patients who are deemed high risk of fall.**

- **COVID Telehealth Follow-up:**
  - **Telehealth follow up visits are available through the following teams:**
    - **PCPs if the patient has a VUMC PCP**
    - **Vanderbilt Health OnCall if the patient does not have a PCP or has an external PCP. Appointments may be requested by sending a message to "COVID-19 Admin" InBasket pool.**
    - **Discharging clinicians should place a nurse order in eStar to supply the patient with a pulse oximeter as part of the discharge orders.**

Outpatient Care

13. General Recommendations for Care and Follow-up of COVID-19 Positive Outpatients Who Have Not Been Hospitalized for COVID-19

- **General Care:**
  - When possible, patients with symptoms consistent with COVID-19 should be triaged via telehealth visits before receiving in-person care.
  - Management should be based on patient's vital signs, physical exam, risk factors for progression to severe illness, and availability of health care resources.
  - Symptomatic management may include hydration, antipyretic medications, analgesic medications, and antitussive medications as needed.
  - All patients with hypoxia (i.e., SpO2 <90% on room air) or symptoms suggesting higher acuity (e.g., new, or worsening dyspnea, mental status changes, central chest pain, blue lips) should be referred for acute care evaluation. Patients should be counseled regarding development of these symptoms which may warrant reevaluation.
- **See the COVID-19 Therapeutic Locator for non-Vanderbilt care locations at https://covid-19-therapeutics-locator-dhhs.hub.arcgis.com/**
- **Oral Antivirals for COVID-19 Treatment**
  - See Section 14 for further details.
- **Monoclonal Antibody Treatment**
  - See Section 15 for further details.
- **Antibiotic Treatment**
  - Only begin antibiotics in outpatients who have strong evidence of a bacterial infection by exam or testing.
  - NOTE: Typical COVID-19 symptoms alone, such as fever and cough, are generally not an indication for antibiotics.
  - For outpatients who present with a biphasic illness or persistent worsening of symptoms after several days of COVID-19 illness, clinicians may consider ordering a stat serum procalcitonin to help determine need for antibiotics.
    - For outpatients with a serum procalcitonin value >0.5 µg/L, patients should be strongly considered for antibiotic therapy and followed closely for signs of worsening disease.
- **Corticosteroid Treatment:**
  - Outpatients with documented room air oxygen saturations of <90% who decline acute care evaluation or hospitalization may be considered for oral corticosteroid therapy, as noted in Section 3.
  - Inhaled corticosteroids are not currently recommended for treatment of symptomatic outpatients by the NIH COVID-19 Treatment Guidelines or IDSA Guidelines. Inhaled corticosteroids are currently being evaluated in clinical trials for symptomatic outpatients.
    - If a provider chooses to prescribe inhaled corticosteroids based on currently available data, budesonide 180 mcg/actuation 4 puffs twice a day for 7 days (or until symptoms resolve) may be considered for symptomatic outpatients with room air oxygen saturations ≥90%.
    - If oral corticosteroids are combined with a strong CYP3A4 (such as the ritonavir component of Paxlovid™), closely monitor for signs and symptoms of corticosteroid excess.
    - If budesonide is not available, other inhaled corticosteroid alternatives include:
      - Beclomethasone 400 mcg twice a day for 7 days
      - Ciclesonide 320 mcg twice a day for 7 days
      - Fluticasone propionate 500 mcg twice a day for 7 days
      - Mometasone 400 mcg (MDI) or 440 mcg (DPI) twice a day for 7 days
- **Other Treatments**
  - See Section 23 for a list of medications that should not be started for protection against or treatment of COVID-19 unless in the context of an approved clinical trial.
- **Clinical Trial Information**
  - The ACTIV-6 trial is recruiting nationally and testing FDA-approved repurposed medication for mild to moderate COVID-19. Currently enrolling treatment arms include fluvoxamine and

ivermectin. . Additional information is available at https://activ6study.org. Adults age 30 or older may be referred via the Vanderbilt Coordinating Center at 615-353-8010 or via email at vcc@vumc.org.

- **VTE Prophylaxis:**
  - Do not start VTE prophylaxis in patients with COVID-19, unless in the context of an approved clinical trial or the presence of other indications.
  - See Section 12 for information for patients discharged and meeting criteria for High Intensity C2H.
- **Outpatient Isolation:**
  - Patients who test positive for COVID-19 should self-isolate x 5 days after the test was obtained AND until improving and fever-free x 24 hours unless the patient is immunocompromised*. Patients should continue to wear a mask around other for 5 additional days. This is recommended regardless of vaccination status.
  - Patients who are immunocompromised* and test positive for COVID-19 should self-isolate x 20 days after the test was obtained AND until improving and fever-free x 24 hours. This is recommended regardless of vaccination status.
  - * Immunocompromise is defined as one or more of the following:
    - Primary immune deficiency (such as CVID)
    - HIV infection with CD4 count ≤200 cells/µL
    - Solid or stem cell organ transplant
    - Chemotherapy in the past year
    - Biologic immunosuppressants (e.g., monoclonal antibody therapy for autoimmune diseases)
    - ≥ 20 mg/day prednisone for ≥ 14 days
- **Follow-up:**
  - Advanced practice providers from Vanderbilt Health OnCall will perform patient consultation via telephone or telemedicine on an as needed basis for patients who do not have a PCP.
  - For patients of high concern who are discharged from a VUMC walk-in clinic or ED with a pending COVID-19 test, a home health consultation may be placed, and the patient will be directly followed by home health.
  - Patients may be seen in-person in any VUMC clinic after they have completed their period of self-isolation. Patients should be instructed to wear a surgical mask if they continue to have respiratory symptoms at the time of their appointment.
  - Most patients do NOT need follow-up COVID-19 testing after a positive result. Exceptions may include patients requiring immune suppression or other medical interventions.
- **Outpatient Panel Flags:**
  - If clinicians and staff would like to view a patient's COVID-19 status in their outpatient panel, follow the instructions on how to add the Infection/Isolation flag to the outpatient panel in eStar using the following link: Customizing Your Schedule with COVID-19 Status. The COVID-19 flag will generally remain on a patient's chart for at least 20 days after a positive SARS-CoV-2 PCR result.

14. Recommendations for Outpatient Antivirals for COVID-19 Treatment

If a provider chooses to prescribe an oral antiviral product for COVID-19 treatment that has been authorized by the FDA, nirmatrelvir/ritonavir (Paxlovid™) should be preferred if clinically appropriate AND available over other options. See sections below for specific details for each medication.

COVID-19 Therapeutics Locator. (https://covid-19-therapeutics-locator-dhhs.hub.arcgis.com/) Pharmacies with availability may not be the closest pharmacy to patient's zip code. If product is available based on the link above, call the pharmacy to confirm availability prior to prescribing.

Patients admitted to the hospital during their course of COVID-19 oral antivirals should use their home supply, per the provider's discretion.
Combined use of nirmatrelvir/ritonavir, molnupiravir, and/or remdesivir is NOT recommended.

Drug/drug interactions may occur with anti-viral treatments for COVID-19. Providers are encouraged to assess for drug/drug interactions prior to treating a patient with these therapies. https://covid19-druginteractions.org/checker

The below criteria are based on the FDA EUA for each product as well as the Tennessee Department of Health guidance.

Paxlovid™ (nirmatrelvir tablets; ritonavir tablets; co-packaged)

- The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of the unapproved product Paxlovid™ (nirmatrelvir tablets; ritonavir tablets; co-packaged) for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric individuals (12 years of age and older weighing at least 40 kg).
- Per the EUA, Paxlovid™ is authorized for patients with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.
- Paxlovid™ is not approved for any use, including for use as treatment of COVID-19. The following guidance is provided to assist providers who choose to prescribe Paxlovid™ for authorized use.
- Limitations of Authorized Use:
    - Paxlovid™ is not authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19.
        - NOTE: Patients hospitalized for reasons for other indications who have mild-to-moderate COVID-19 that would not have required hospitalization may be treated with Paxlovid™ to decrease the risk of future progression, hospitalization, and/or death.
        - NOTE: Patients treated with Paxlovid™ who progress to severe COVID-19 requiring hospitalization may complete 5 days of treatment, at the provider's discretion.
    - Paxlovid™ is not authorized for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.
    - Paxlovid™ is not authorized for use longer than 5 consecutive days.
- Paxlovid™ may decrease the risk of progression to severe COVID-19, including hospitalization or death, in people with at least one of the following risk factors:
    - Age > 60
    - Diabetes
    - Overweight (BMI>=25)
    - Chronic lung disease (including asthma)
    - Chronic kidney disease
    - Current smoker
    - Immunosuppressive disease or immunosuppressive treatment
    - Cardiovascular diseases
    - Hypertension
    - Sickle cell disease
    - Neurodevelopmental disorders
    - Active cancer
    - Medically-related technological dependence

    - NOTE: Patients with other risk factors for disease progression may benefit from treatment but were not reflected in clinical studies at time of EUA.
    - NOTE: Patients who had a history of prior COVID-19 infection or vaccination were excluded in available clinical studies at time of EUA.
- Dosage and Administration:
    - Initiate as soon as possible after diagnosis of COVID-19 and within 5 days of symptoms onset.
    - Patients may take Paxlovid™ orally with or without food. Advise patients to swallow all tablets for Paxlovid™ whole and not to chew, break, or crush the tablets.
    - Dosage: 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet), with all three tablets taken together twice daily for 5 days.
    - If the patient misses a dose by more than 8 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. The patient should not double the dose to make up for a missed dose
    - Renal and Hepatic Dosing:
        - Dose reduction for moderate renal impairment (eGFR≥30 to <60 mL/min):
            - 150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet), with both tablets taken together twice daily for 5 days.
        - Severe renal impairment (eGFR<30 mL/min):
            - Paxlovid™ is not recommended in patients with severe renal impairment.
        - Severe hepatic impairment:
            - Paxlovid™ is not recommended in patients with severe hepatic impairment (Child-Pugh Class C).
- Contraindications:
    - History of clinically significant hypersensitivity to the active ingredients (nirmatrelvir or ritonavir) or any other components.
    - Co-administration with drugs highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions.
    - Co-administration with potent CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance.
    - NOTE: Recent or concurrent monoclonal antibody treatment is not a contraindication to COVID-19 oral antiviral treatment.
- Monitoring:
    - No laboratory monitoring indicated
    - Co-administration of Paxlovid™ with other CYP3A substrates may require a dose adjustment or additional monitoring as shown in the Fact Sheet for Healthcare Providers.
    - Consider using a drug-drug interaction tool (https://covid19-druginteractions.org/checker) or consulting with a pharmacist to identify drug-drug interactions and associated dose adjustments.
- Adverse Effects and Precautions:
    - Hypersensitivity reactions have been reported with Paxlovid™ including urticaria, angioedema,
    - dyspnea, mild skin eruptions, and pruritus. Cases of anaphylaxis, toxic epidermal necrolysis, and Stevens-Johnson syndrome have also been reported with ritonavir, a component of Paxlovid™.
    - Dysgeusia
        - NOTE: Providers should counsel patients prescribed Paxlovid™ that abnormal or altered taste may be a medication side effect rather than a symptom of COVID-19.
    - Diarrhea
    - Hypertension
    - Myalgia
- Precautions and Additional Considerations:
    - The concomitant use of Paxlovid™ and certain other drugs may result in potentially significant drug interactions. https://covid19-druginteractions.org/checker
    - Hepatic transaminase elevations, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir
    - HIV-1 drug resistance to HIV protease inhibitors may occur in individuals with uncontrolled or undiagnosed HIV-1 infection.

- There are no available human data on the use of nirmatrelvir (component of Paxlovid™) during pregnancy to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.
- 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.
- Use of ritonavir may reduce the efficacy of combined hormonal contraceptives. Advise patients using combined hormonal contraceptives to use an effective alternative contraceptive method or an additional barrier method of contraception.
- **Per a CDC advisory (https://emergency.cdc.gov/han/2022/pdf/CDC_HAN_467.pdf), COVID-19 rebound has been reported to occur between 2 and 8 days after initial recovery and is characterized by a recurrence of COVID-19 symptoms or a new positive viral test after having tested negative. A brief return of symptoms may be part of the natural history of SARS-CoV-2 (the virus that causes COVID-19) infection in some persons, independent of treatment with Paxlovid™ and regardless of vaccination status. Limited information currently available from case reports suggests that persons treated with Paxlovid™ who experience COVID-19 rebound have had mild illness; there are no reports of severe disease. There is currently no evidence that additional treatment is needed with Paxlovid™ or other anti-SARS-CoV-2 therapies in cases where COVID-19 rebound is suspected.**

- Prescribing and Reporting:
  - If prescribed, the Paxlovid™ EUA Fact Sheet for Patients, Parents, and Caregivers must be provided to the patient and/or caregiver at time of prescription, and documentation that it was reviewed with the patient and/or caregiver must be placed in the clinical record.
  - Serious adverse events believed to be related to Paxlovid™ should be reported to FDA MedWatch within 7 days of event.

Lagevrio™ (Molnupiravir)

- The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of the unapproved product Lagevrio™ (molnupiravir) for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults.
- Per the EUA, molnupiravir is authorized for patients with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, ***and for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate.***
- Molnupiravir is not approved for any use, including for use as treatment of COVID-19. The following guidance is provided to assist providers who choose to prescribe molnupiravir for authorized use.
- Limitations of Authorized Use:
  - Molnupiravir is not authorized for use in patients less than 18 years of age.
  - Molnupiravir is not authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19.
    - NOTE: Patients hospitalized for reasons for other indications who have mild-to-moderate COVID-19 that would not have required hospitalization may be treated with molnupiravir to decrease the risk of future progression, hospitalization, and/or death.
    - NOTE: Patients treated with molnupiravir who progress to severe COVID-19 requiring hospitalization may complete 5 days of treatment, at the provider's discretion.
  - Molnupiravir is not authorized for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.
  - Molnupiravir is not authorized for use longer than 5 consecutive days.
- Molnupiravir may decrease the risk of progression to severe COVID-19, including hospitalization or death, in people with at least one of the following risk factors:
  - Age > 60
  - Diabetes
  - Overweight (BMI≥30)
  - Chronic obstructive pulmonary disease
  - Chronic kidney disease
  - Serious heart conditions

    - Active cancer
    - NOTE: Patients with other risk factors for disease progression may benefit from treatment but were not reflected in clinical studies at time of EUA.
    - NOTE: Patients who were vaccinated against SARS-CoV-2 were not included in available clinical studies at time of EUA.
- Dosage and Administration
    - Initiate as soon as possible after diagnosis of COVID-19 and within 5 days of symptoms onset.
    - Patients may take molnupiravir orally with or without food. Advise patients to swallow all capsules whole and not to chew, break, or crush the capsules.
    - Dosage: 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days.
    - If the patient misses a dose by more than 10 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. The patient should not double the dose to make up for a missed dose.
    - Renal and Hepatic Dosing:
        - No dosage adjustment in patients with any degree of renal impairment is recommended.
        - No dosage adjustment in patients with hepatic impairment is recommended.
- Contraindications:
    - No contraindications have been identified based on the limited available data at time of EUA.
    - NOTE: Recent or concurrent monoclonal antibody treatment is not a contraindication to COVID-19 oral antiviral treatment.
- Monitoring:
    - No laboratory monitoring indicated
- Adverse Effects:
    - Erythema, rash, or urticaria
    - Potential for serious hypersensitivity reaction, including anaphylaxis and angioedema
    - Diarrhea
    - Nausea
    - No drug interactions have been identified based on the limited available data at time of the EUA.
- Precautions and Additional Considerations:
    - The use of molnupiravir is **not recommended** during pregnancy due to the risk of embryo-fetal toxicity. The prescribing provider must assess whether individuals of childbearing potential are pregnant (e.g., pregnancy test assessment), as applicable. Advise individuals of childbearing potential to use effective 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 individuals 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.
    - Breastfeeding is **not recommended** during treatment and for 4 days after the last dose of molnupiravir. A lactating individual may consider interrupting breastfeeding and may consider pumping and discarding breast milk during treatment and for 4 days after the last dose of molnupiravir.
    - Molnupiravir is **not authorized** for use in patients less than 18 years of age because it may affect bone and cartilage growth.
- Prescribing and Reporting:
    - If prescribed, the molnupiravir EUA Fact Sheet for Patients, Parents, and Caregivers must be provided to the patient and/or caregiver at time of prescription, and documentation that it was reviewed with the patient and/or caregiver must be placed in the clinical record.
    - Serious adverse events believed to be related to molnupiravir should be reported to FDA MedWatch within 7 days of event.

Remdesivir

- Early administration of remdesivir has been found to reduce progression to severe COVID-19 in outpatients with at least one risk factor for disease progression (i.e., age ≥60 years, obesity, or certain coexisting medical conditions) if administered within 7 days of symptom onset. (https://www.nejm.org/doi/full/10.1056/NEJMoa2116846)
- For outpatients who have mild-to-moderate COVID-19, are at high risk of progression to severe COVID-19 disease, and who cannot access other authorized therapies, remdesivir may be administered in a monitored medical environment:
    - Loading dose 200 mg IV x 1 then 100 mg IV q24h x 2 days (for a total of 3 days of therapy)
- Monitoring:
    - CMP at baseline and as needed
    - CBC and INR if clinically indicated
    - Monitor patients during infusion and observe patients for at least one hour after infusion is complete for signs and symptoms of hypersensitivity as clinically appropriate.
- For other information regarding remdesivir, including adverse effects, precautions, and contraindications, see Section 2.

NOTE: *Combined use of nirmatrelvir/ritonavir, molnupiravir, and/or remdesivir is NOT currently recommended.*

15. Recommendations for Monoclonal Antibody Treatment in Outpatients with COVID-19

- **Supply of monoclonal antibodies is currently severely limited. Only patients with severe immunosuppression are currently able to receive this treatment.**
- For patients ≥12 years old and at least 40 kg with symptomatic COVID-19 (e.g., respiratory symptoms not requiring supplemental oxygen, cough, anosmia, change of taste, gastrointestinal symptoms), monoclonal antibody treatment has been authorized through an Emergency Use Authorization by the Food and Drug Administration (FDA) for treatment of COVID-19 infected patients.
- Monoclonal antibody treatment is limited to the COVID Infusion Clinic or to inpatients diagnosed with mild-to-moderate COVID-19 but admitted for other medical indications. Patients should not be sent to ED or admitted solely for monoclonal antibody infusion.
- Patients with a positive SARS-COV-2 direct test (PCR or rapid antigen) may be eligible for monoclonal antibody infusion if they meet the following criteria
    - ≤7 days of symptoms;
    - Not on supplemental O2 or not on an increased O2 volume compared to baseline;
    - A medical condition that increases risk of severe disease based on EUA criteria, with more restrictive criteria applied when supply is limited, including:
        - Age ≥65 years
        - Pregnancy
        - Age 18 – 64 and one of the following:
            - Body mass index (BMI) ≥35
            - Immunosuppressive disease
                - HIV infection with CD4 count ≤200 or a diagnosis of AIDS related to prior opportunistic infection
                - Solid organ or stem cell transplant
                - Primary immunodeficiency, such as common variable immunodeficiency or hypogammaglobulinemia
                - Asplenia
                - Sickle Cell Disease or related disorder such as thalassemia
            - Receiving immunosuppressive treatment
                - Chemotherapy in the past year
                - Immunosuppressant use for autoimmune disease
                - Prednisone = 20 mg/day (or equivalent) for ≥14 days

        - Chronic kidney disease defined as GFR <60
        - Diabetes
        - Cardiovascular disease
            - Congenital heart disease
            - Coronary artery disease
            - Congestive heart failure
            - Cerebrovascular disease
            - Hypertension
        - Chronic lung disease
            - COPD
            - Asthma (moderate to severe)
            - Interstitial lung disease
            - Cystic fibrosis
            - Pulmonary hypertension
        - Neurodevelopmental disorders
            - Cerebral palsy
            - Other conditions that confer medical complexity – genetic or metabolic syndromes
            - Severe congenital anomalies
        - Medical-related technological dependence
            - Tracheostomy
            - Gastrostomy
            - Positive pressure ventilation – not related to COVID
    - Other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19 and authorization of monoclonal antibody infusion under the EUA is not limited to the medical conditions or factors listed above. For additional information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html
- Contraindications:
    - New oxygen requirement or increase in baseline O2 requirement
    - NOTE: Prior receipt of monoclonal antibody for COVID-19 infection >30 days ago or prior COVID-19 vaccination is not a contraindication.
    - NOTE: Recent or concurrent COVID-19 oral antiviral treatment is not a contraindication to monoclonal antibody treatment.
- Monitoring:
    - No laboratory monitoring indicated
- Adverse Effects and Precautions:
    - Potential for serious hypersensitivity reaction, including anaphylaxis
    - Infusion related reactions
    - Symptoms including nausea, diarrhea, dizziness, headache, pruritus, and vomiting were observed in clinical trials, though at rates comparable to placebo.
    - NOTE: COVID-19 vaccination can be given at any interval following receipt of passive antibody therapy.
- Referrals, Appeals, Scheduling, and Ordering:
    - Outpatients who have a positive SARS-CoV-2 PCR resulted in eStar will be automatically screened for eligibility and contacted by the COVID-19 infusion clinic if they meet criteria.
    - To refer an outpatient for monoclonal antibody infusion, VUMC providers should send a message with the patient's duration of symptoms, vaccine status (fully vs partially/none), and qualifying criteria to the following eStar in-basket: VUMC COVID19 Infusion Clinical pool basket (p covid inf clinical). If the patient does not have test results available in eStar, they will be asked to show evidence of their positive SARS-CoV-2 (COVID-19) direct viral test prior to infusion.

    - Patients should not be directed to the VUMC Emergency Department in order to receive COVID-19 monoclonal antibody infusion, as it is not available in the ED.
    - Appeal requests for administration of monoclonal antibody in outpatients who do not meet criteria, should be made through the VUMC COVID-19 Infusion Clinical Basket, and will be escalated through the established VUMC PT&D appeal for restricted medication process.
    - The EUA Fact Sheet will be provided to the patient and/or caregiver at the time of infusion and documentation that it was reviewed will be placed in the clinical record (EUA Fact Sheet details and safety information).
- Medication errors and/or serious adverse events believed to be related to monoclonal antibody administration should be reported to the VUMC Pharmacy, who will assist with submitting the required FDA MedWatch reports within 7 days of event.

16. Recommendations for Evusheld™ (tixagevimab co-packaged with cilgavimab) for COVID-19 Pre-exposure Prophylaxis

- The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of the unapproved product Evusheld™ (tixagevimab co-packaged with cilgavimab) for the pre-exposure prophylaxis of coronavirus disease 2019 (COVID-19) in adults and pediatric individuals (12 years of age and older weighing at least 40 kg)
- This therapy is only authorized in those who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2.
- Per the EUA, Evusheld™is authorized for patients who:
    - Have moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments and may not mount an adequate immune response to COVID-19 vaccination, or
    - Have a history of severe adverse reaction (e.g., severe allergic reaction) to a COVID-19 vaccine(s) and/or COVID-19 vaccine component(s)
- Due to limited supply of this therapy, priority for receipt of Evusheld™at VUMC will be given to patients at highest risk of complication from COVID-19 who are the least likely to generate an effective immunologic response to COVID-19. This guidance has been adapted from the Minnesota Department of Health Interim Ethical Framework for Allocation of Tixagevimab/Cilgavimab during the COVID-19 Pandemic (https://www.health.state.mn.us/diseases/coronavirus/hcp/therapeutic.html).
- SARS-CoV-2 antibody testing is not included as a means of prioritizing patients at this time, due to a lack of data on the degree of protection and correlates of immunity with serological assays.
- **At this time, Category 1, 2, 3, and 4 patients may be referred for consideration of therapy. Patients in category 5 may be referred as an appeal with documentation support as to the rationale for vaccine allergy or contraindications.**
- Eligibility Categories
    - Category 1
        - Lung transplant recipient (any time frame).
        - Small bowel transplant recipient (any time frame).
        - Receipt of the following immunosuppressive medication within the past 12 months (including for solid organ transplant).
            - Anti-thymocyte globulin (ATG)
            - Alemtuzumab
            - Basiliximab
            - Anti-B-cell therapy, including:
                - Anti-CD20
                - Anti-CD19
                - Anti-CD38
                - Anti-79a
                - BTK inhibitors
                - PI3K inhibitors
                - Venetoclax

        - S1P inhibitor medications (e.g., fingolimod, siponimod, ponesimod, ozanimod)
    - B-cell malignancies, on active treatment or within 1 month of last treatment (excluding immunosuppressive medications listed above; e.g., B-cell lymphomas, chronic lymphocytic leukemia, acute B-cell lymphoblastic leukemia, etc.).
    - Multiple myeloma, on active treatment with two or more agents or within 1 month of last treatment (excluding immunosuppressive medications listed above).
    - Allogeneic stem cell transplant, within 12 months of transplant.
    - Autologous stem cell transplant, within six months of transplant.
    - Receipt of anti-CD19 or anti-BCMA (CAR)-T-cell immunotherapy, within six months of treatment.
    - Primary or secondary T-cell immunodeficiency, including severe combined immunodeficiency.
    - Recipient of more than one active transplant, different organs (any time frame).
        - Example: kidney-pancreas, heart-kidney
    - Acute myeloid leukemia, on active treatment or within 1 month of last treatment (excluding immunosuppressive medications listed above)
- Category 2
    - Any solid organ transplant within the past 12 months from date of transplant, not otherwise eligible in Category 1.
    - Allogeneic stem cell transplant, more than 12 months since transplant.
    - Autologous stem cell transplant, more than 6 months since transplant.
- Category 3
    - Any solid organ transplant recipient more than 12 months since transplant, not otherwise eligible in Categories 1 or 2.
    - Any solid tumor, on active myelosuppressive chemotherapy or within 1 month of last treatment (excluding immunosuppressive medications listed above).
    - Multiple myeloma, on maintenance therapy (excluding immunosuppressive medications listed above).
- Category 4
    - Active treatment with high-dose corticosteroids (i.e., more than 20 mg prednisone or equivalent per day when administered for two weeks or longer).
    - Active treatment with other biologic agents that are immunosuppressive or immunomodulatory or within 3 month of last treatment, not otherwise listed in Categories 1-3.
    - Advanced or untreated HIV infection.
        - HIV with CD4 less than 200/mm3 (if aged less than 14 years, CD4% less than 15%)
        - AIDS-defining illness
- Category 5
    - Persons for whom vaccination with any available COVID-19 vaccine, according to the approved or authorized schedule, is not recommended, due to a history of severe adverse reaction (e.g., severe allergic reaction) to a COVID-19 vaccine(s) and/or COVID-19 vaccine component(s).
    - Prior to treatment with Evusheld™, patients should be evaluated for vaccine and/or vaccine component allergy or adverse effect by Vanderbilt Allergy.

- Contraindications:
    - Prior hypersensitivity reactions, including anaphylaxis, to any component of Evusheld™ (i.e., tixagevimab, cilgavimab, L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80, sucrose)
    - NOTE: Evusheld™is not authorized for use in individuals:
        - For treatment of COVID-19
        - For post-exposure prophylaxis of COVID-19
    - **NOTE: Pre-exposure prophylaxis with Evusheld™ is not a substitute for vaccination in individuals for whom COVID-19 vaccination is recommended. Vaccination with a complete primary series and boosting is strongly recommended for patients at risk of**

severe COVID-19. Vaccinations should not be delayed by the anticipated or planned administration of Evusheld™.
    - **NOTE: Patients who have been recently vaccinated should wait 14 days prior to Evusheld™administration.**
- Dosage and Administration
    - 300 mg of tixagevimab
    - 300 mg of cilgavimab
    - Administered as separate consecutive intramuscular injections at different injection sites (preferably one in each of the gluteal muscles)
    - The SARS-CoV-2 variants that will be circulating in the United States when Evusheld™may need to be redosed are not known at this time and therefore repeat dosing recommendations cannot be made; the Fact Sheets will be revised with repeat dosing recommendations in the future when more data are available.
    - The FDA revised the EUA on February 24, 2022, to change the dose from 150 mg of tixagevimab and 150 mg of cilgavimab to 300 mg of tixagevimab and 300 mg of cilgavimab. For patients who initially received 150 mg tixagevimab and 150 mg cilgavimab:
        - Initial dose ≤3 months prior: 150 mg tixagevimab and 150 mg cilgavimab.
        - Initial dose >3 months prior: 300 mg tixagevimab and 300 mg cilgavimab.
- Monitoring:
    - No laboratory monitoring indicated
    - Patients receiving Evusheld™should be clinically monitored for at least one hour after the receipt of the injections.
- Adverse Effects and Precautions:
    - Potential for serious hypersensitivity reaction, including anaphylaxis
    - Headache
    - Fatigue
    - Cough
    - As with any intramuscular injection, Evusheld™should be given with caution to individuals with thrombocytopenia or any coagulation disorder.
    - A higher proportion of subjects who received Evusheld™versus placebo reported myocardial infarction and cardiac failure serious adverse events (SAEs). All subjects who experienced cardiac SAEs had cardiac risk factors and/or a prior history of cardiovascular disease at baseline. A causal relationship has not been established.
    - There are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Evusheld™should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus.
- Referrals and Ordering:
    - For outpatients:
        - To refer an outpatient for consideration for Evusheld™, complete the following steps as per Evusheld™ ordering tipsheet:
            - Open an orders-only encounter in eStar for the eligible patient and responsible provider/department.
            - Navigate to the therapy plan tab in the patient's chart.
            - Assign the plan the first available therapy plan slot.
            - Enter the desired plan start date, lead provider, anticipated treatment location, and associate with the diagnosis that corresponds with their eligibility.
            - Review the orders within the therapy plan. Follow the instructions for scheduling the patient after the therapy plan orders are signed.
            - Address the hard stop for the "tixagevimab-cilgavimab (Evusheld™) intramuscular injection 300 mg" order by clicking the order, navigating to the "Note to Pharmacy" field, placing the cursor within the brackets containing the text "{Evusheld Reason for Use Click F2: 40824004}" and clicking F2.
            - This opens a smart list that allows you to provide the required eligible reason for Evusheld™. Of note, if applicable, multiple eligibility criteria are able to be selected from the smart list. This information will be used during order verification at the time of the patient's appointment to determine appropriateness for dispensing.

                - After providing eligibility criteria response, select Accept.
                - Finally, sign the plan to place the orders on the patient's chart. The orders will then be available for release at the time of the patient's appointment. Please remember to follow the steps in the therapy plan for requesting an appointment slot for the patient.
                - If scheduling desired route a communication to EVUSHELD INFUSION SCHEDULING
            - Upon receipt of referral, patient eligibility will be confirmed.
            - Selection of patients for Evusheld™will be based on referral, confirmation of eligibility, and allocation procedures to promote equitable and ethical distribution.
            - Due to limitations of supply, some patients referred for Evusheld™may not be allocated treatment immediately. Patients referred for Evusheld™will be contacted when drug has been allocated for administration.
            - Evusheld™administration will be conducted at a previously designated administration site (e.g., VUMC TVC Infusion Center, VUMC 100 Oaks Infusion Center, Vanderbilt-Ingram Cancer Center Cool Springs Infusion Center).
        - For inpatients:
            - Evusheld™may be administered during hospitalization for patients who meet current eligibility criteria.
            - Hospitalized patients must have a negative COVID PCR test as part of their current hospitalization.
            - Evusheld™should only be ordered and administered within 24 hours of anticipated hospital discharge. Alternatively, patients may be referred for outpatient administration as noted.
            - Evusheld™may be ordered in eStar and will be reviewed for approval.
        - The EUA Fact Sheet should be provided to the patient and/or caregiver and documentation that it was reviewed should be placed in the clinical record.
- Medication errors and/or serious adverse events believed to be related to Evusheld™should be reported to the VUMC Pharmacy, who will assist with submitting the required FDA MedWatch reports within 7 days of event.

17. Repeat COVID-19 PCR Testing in Symptomatic Outpatients

- If an outpatient has a negative COVID-19 antigen test (self-collected or at an outside laboratory), especially early in the course of a clinical illness with high clinical suspicion for COVID-19, it is reasonable to repeat with a PCR test (either Liat or laboratory-based PCR).
- Repeat testing of outpatients with a negative COVID-19 PCR test (either Liat or laboratory-based PCR) is not recommended, as this significantly increases the likelihood of a false positive test result.

18. Adult Post-Acute COVID-19 Clinic

- Patients who are experiencing persistent symptoms more than 4 weeks after a COVID-19 diagnosis can be referred to the Adult Post-Acute COVID Clinic (APACC).
- Patients should be 18 years or older, medically stable for outpatient evaluation and have had a confirmed positive SARS-COV2 PCR or rapid antigen test at least 4 weeks prior to referral.
- Eligible patients without a Vanderbilt PCP will be scheduled with a general internist for an initial telemedicine consultation; referrals will then be coordinated with additional specialties as needed, including autonomics, benign hematology, cardiology, infectious diseases, neurology, ophthalmology, otology, physical medicine & rehabilitation, psychiatry, pulmonary medicine, and/or COVID-specific rehabilitation services through the Dayani Center.
- Referrals can be made by using the "Ambulatory referral to Post-Acute COVID Clinic" order. Patients or referring clinicians can call 615-936-1212. For more information, please visit https://www.vumc.org/coronavirus/PostAcuteCOVIDClinic or contact Sara Martin or Cecelia Theobald.

OTHER COVID-19 RELATED GUIDANCE

19. Guidance for Clearance of Suspected and Confirmed COVID-19 Patients

- Updated recommendations may be found at Guidance for Clearance of Suspected and Confirmed COVID Patients

20. Guidance for Preprocedural/Presurgical COVID-19 PCR Testing

- General COVID-19 testing recommendations may be found at VUMC Guidelines for COVID-19 Testing
- Specific guidance and a preprocedural guide for clearance of COVID-19 patients for surgery may be found at VUMC Guidance for Clearance of COVID Patients for Surgery

21. Guidelines for COVID-19 PCR Testing in Asymptomatic Patients

- Updated COVID-19 testing recommendations may be found at VUMC Guidelines for COVID-19 Testing

22. Guidelines for COVID-19 IgG Serology Testing

- COVID-19 IgG serology should NOT be ordered to explain a resolved illness consistent with COVID-19, to confirm immunity to COVID-19 following infection or vaccination, or to inform decisions around returning to work or relaxing social distancing. The relationship between COVID-19 IgG and immunity is not yet defined, and a positive COVID-19 IgG result should not be interpreted as protection against infection/reinfection.
- COVID-19 IgG testing is only allowed at VUMC for one of the following approved indications:
    - Suspected multisystem inflammatory syndrome in children or adults (MIS-C and MIS-A)
    - Unexplained myocarditis
    - Unexplained ARDS/severe respiratory illness with negative SARS-CoV-2 PCR
    - Unexplained recently diagnosed vasculitis with negative routine work up
    - Unexplained CNS thrombosis in a patient without risk factors
    - Guidance for adjunctive monoclonal antibody treatment in select clinical scenarios
    - Other clinical situation in which management will change based on test result (must specify)

23. Recommendations for Other Medications Previously Proposed for Treatment of COVID-19

- Do not start or stop these medications solely for protection against or treatment of COVID-19 unless in the context of an approved clinical trial:
    - ACE inhibitors/ARBs
    - Azithromycin
    - Colchicine
    - Fluvoxamine
    - H2-blockers
    - Hydroxychloroquine (hold if previously prescribed and treated with remdesivir)
    - Ivermectin
    - Lopinavir/Ritonavir
    - Sitagliptin/DPP-4 Inhibitor
    - Statins
    - Vitamin C
    - Vitamin D
    - Zinc

24. Postmortem Information

- All COVID-19 related deaths must be reported to the Davidson County Medical Examiner's Office.
    - This process will trigger additional notifications from the Davidson County Medical Examiner's Office to the State Medical Examiner's Office and the health department of the patient's residence.
- When contacting the Davidson County Medical Examiner's Office about other patient deaths, notify their office of all patient infections including positive RPP results for routine coronaviruses.
- For additional information see the COVID-19 Post-Mortem Care SOP available on the VUMC COVID website.
- FEMA will provide up to $9,000 in financial assistance for COVID-19 related funeral expenses for eligible family members. Applications can be made via the COVID-19 Funeral Assistance Helpline at 844-684-6333 and must include an official death certificate attributing the death to COVID-19 as well as funeral expense documents. More information available at https://www.fema.gov/disaster/coronavirus/economic/funeral-assistance.

25. COVID-19 Vaccine Considerations

- **General Side Effects**
    - Patients should be advised that post-vaccine symptoms are common, including the following:
        - Sore arm
        - Fever and/or chills
        - Myalgias/Arthralgias
        - Fatigue
        - Headache
    - Symptoms related to the COVID-19 vaccine typically occur 1-2 days post-vaccination and resolve in 1-2 days. If these symptoms occur later than 2 days post-vaccination or last longer than 2 days, consider referring the patient for COVID-19 testing.
    - Respiratory and GI symptoms are not related to the vaccine, and patients with these symptoms should be evaluated for COVID-19.
    - Patients who have had COVID-19 infection should wait until they have completed self-isolation and their COVID-19 symptoms have improved before receiving vaccination. Patients should be vaccinated within 90 days after their positive COVID-19 test in order to maintain protection against re-infection with COVID-19.
- **Thrombosis with Thrombocytopenia Syndrome (TTS) (Vaccine-Induced Immune Thrombotic Thrombocytopenia {VITT})**
    - This is a rare syndrome with clinical and laboratory findings similar to heparin-induced thrombocytopenia (HIT).
    - TTS has been recognized as a rare complication of the AstraZeneca and Johnson & Johnson adenoviral vaccines, but it is unclear if the syndrome occurs as a result of the Moderna and Pfizer mRNA vaccines.
    - Criteria for diagnosis:
        - COVID vaccine 4 – 42 days prior to symptom onset
        - Any venous or arterial thrombosis (often cerebral or abdominal)
        - Thrombocytopenia (i.e., platelet count < 150 cells/μL)
        - Positive HIT ELISA test
        - Markedly elevated D-dimer (> 4 times the upper limit of normal; may not be observed in all patients at presentation)
    - Evaluate urgently for TTS if the following develop within 4 to 42 days after vaccination:
        - Severe persistent headache, visual changes, or seizure like activity, which may be symptoms of cerebral venous sinus thrombosis
        - Severe, persistent abdominal pain, which may be a symptom of abdominal venous thrombosis
        - Leg swelling or pain
        - Chest pain or shortness of breath

        - Petechiae, easy bruising, or bleeding
    - Evaluation:
        - CBC with platelets
        - CMP
        - PT/INR, PTT, fibrinogen
        - D-dimer quantitative
        - HIT ELISA
        - Imaging for thrombosis based on signs and symptoms
    - Treatment:
        - If there is evidence of thrombosis AND thrombocytopenia (i.e., platelets < 150,000 cells/µL) or markedly elevated D-dimer, or both:
            - Admit to hospital
            - Consult benign hematology
            - Do NOT administer heparin or enoxaparin anticoagulant
            - Treat with argatroban or bivalirudin
            - Avoid platelet transfusion
        - If there is evidence of thrombosis with a normal platelet count (i.e., platelets ≥ 150,000 cells/µL) and D-dimer is not markedly elevated:
            - Contact benign hematology on-call
            - Do NOT administer heparin or enoxaparin anticoagulant
            - Treat with apixaban, rivaroxaban, or another non-heparin anticoagulant
        - If there is evidence of new thrombocytopenia (platelets < 150,000) without thrombosis:
            - Contact benign hematology on-call
            - Admit if there is evidence of coagulopathy (e.g., low fibrinogen, elevated D-dimer, abnormal PT/INR or PTT)
            - Admit if platelets < 30,000 cells/µL
            - Admit if patient is bleeding
- **Vaccine-Induced Immune Thrombocytopenic Purpura (ITP)**
    - This can occur after any COVID-19 vaccine, including those made by Moderna, Pfizer, AstraZeneca or Johnson & Johnson.
    - Criteria for diagnosis:
        - Patients who received any COVID-19 vaccine in the past 30 days (median 8 days) with:
            - New thrombocytopenia (NOTE: platelets may be as low as <10,000 cells/µL)
            - No thrombosis
            - Normal PT/INR, PTT, fibrinogen, and D-dimer
    - Evaluation:
        - CBC with platelets
        - CMP
        - PT/INR, PTT, fibrinogen
        - D-dimer quantitative
        - HIT ELISA
    - Treatment:
        - Consult benign hematology (who may recommend IVIG and/or corticosteroids)
        - Admit if platelets < 30,000 cells/µL and/or bleeding