OUTPATIENT GUIDANCE FOR TREATMENT OF COVID-19 IN ADULTS AND CHILDREN

These are interim treatment recommendations based on best available evidence at this time. Recommendations may be modified based on resource availability, testing recommendations, and future published data.

Clinical symptoms range from uncomplicated upper respiratory tract viral infection to pneumonia, acute respiratory distress syndrome (ARDS), sepsis, and septic shock.

Testing:
See link to current COVID-19 testing recommendations: Send testing for COVID-19

Treatment:
1. Supportive care:
   Supportive care is the mainstay of treatment for non-hospitalized patients.

2. Inhaled corticosteroids:
Inhaled budesonide (800 mcg BID x14 days) and ciclesonide (320 mcg BID x30 days) have been studied in non-hospitalized adults with mild-moderate symptoms of COVID-19. The results of these studies do not demonstrate a consistent impact of inhaled corticosteroid therapy on time to recovery of COVID-related symptoms. Similarly, inhaled corticosteroid therapy reduced COVID-related emergency-department visits or hospitalizations in some studies but not others. As such, while we do not recommend inhaled corticosteroids as routine therapy, they may be considered on a case-by-case basis given some potential for benefit and a low risk of harm. Studies to date have not identified an optimal product or dose. While short-term inhaled corticosteroid therapy in COVID-19 patients has been shown to be relatively safe in studies to date, budesonide, ciclesonide, and fluticasone are all CYP3A4 substrates, and concomitant administration with potent CYP3A4 inhibitors such as azole antifungals, ritonavir, cobicistat, and clarithromycin (among others) may result in symptoms of corticosteroid excess. Such co-administration is not recommended.

3. Monoclonal antibody infusion:
The FDA has issued an EUA for sotrovimab for non-hospitalized adults and adolescents (12-17 years old) with mild to moderate symptoms of COVID-19 with risk factors for progression to severe disease (see Michigan Medicine Eligibility Criteria). This is a monoclonal antibody that has been developed to bind to the spike protein of SARS-CoV-2 and block the virus from invading human cells. Research suggests that it may reduce the chances that high-risk patients with mild to moderate COVID-19 will develop severe disease that requires a visit to the emergency department and/or hospitalization.

   The goal is to give the medication as early in the course of disease as possible. The criteria utilized to identify patients with risk factors for severe disease have been approved by the Scarce Resource Allocation Committee and will be re-evaluated based on drug supply and infusion capacity.

   A clinician must place a “Referral for COVID-19 Monoclonal Antibody Treatment” order, which will go directly to the COVID mAb trained pharmacy team. If a patient is potentially eligible and capacity allows, the patient will be contacted to discuss symptom duration and consent and proceed with scheduling the infusion based on capacity available. Primary care physicians will be notified if their patient is contacted to discuss the infusion. Due to the overwhelming demand, not all patients referred will be able to be treated. Patients can also be referred to the MDHHS COVID Therapeutics webpage to seek out other sites for possible treatment.

   Patients will receive the medication IV as an approximately 30-minute infusion. One hour of observation afterwards is required. Rarely, patients could experience an allergic reaction or an infusion-related reaction during the infusion (~1% in the COMET-ICE study).

   The most common reported symptoms after the infusion are nausea, diarrhea, dizziness, vomiting, myalgias, headache, and malaise. These symptoms did not occur more frequently in patients receiving the monoclonal antibody infusion when compared to the placebo group. Thus, for most patients such symptoms are more likely to be related to COVID-19 rather than the infusion. Patients receiving a monoclonal antibody infusion are also still at risk for progression to severe disease.
Therefore, a patient complaining of worsening shortness of breath in the few days following the infusion could be experiencing COVID-19 progression or a delayed reaction to the infusion. Irrespective of the underlying cause, they should be evaluated urgently. Patients without shortness of breath or other concerns requiring emergent evaluation in the ED can be managed with supportive care (i.e., ibuprofen, acetaminophen, fluids, anti-emetics, loperamide).

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<tr>
<th>Michigan Medicine Monoclonal Antibody Eligibility Criteria*</th>
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<td>A patient must have had a Michigan Medicine encounter in the last 5 years OR be a Michigan Medicine employee OR be a University of Michigan student OR be a resident of Washtenaw County</td>
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Patients with mild or moderate COVID-19 who meet criteria #1-4 AND either criteria #5, #6, OR criteria #7:

1. Outpatient
2. No requirement for supplemental oxygen (or no increase from baseline supplemental oxygen)
3. Symptoms ≤10 days
4. Not received convalescent plasma
5. Not fully vaccinated Adult ≥18 years old and ≥40 kg AND one of the following:
   a) BMI ≥35
   b) Age ≥65
   c) Chronic respiratory disease (e.g., COPD, moderate or severe asthma (requires daily inhaled corticosteroid), bronchiectasis, CF, ILD)
   d) Cardiovascular disease (e.g., HTN, valvular disease, CVA, PAD, CHF)
   e) Diabetes
   f) CKD (stage III, IV, or end stage CKD GFR <15 or dialysis)
   g) Immunosuppressed: congenital or acquired immunodeficiency, SOT, active malignancy receiving chemotherapy, BMT, or autoimmune diseases requiring immunosuppressive therapy, splenectomy, sickle cell disease (auto-splenectomy), Down Syndrome
   h) Pregnancy
6. Vaccinated Adult ≥18 years old and ≥40 kg AND one of the following:
   a) BMI ≥35
   b) Age ≥65
   c) Chronic respiratory disease (e.g., COPD, moderate or severe asthma (requires daily inhaled corticosteroid), bronchiectasis, CF, ILD)
   d) On Renal replacement therapy (hemodialysis or peritoneal dialysis)
   e) Immunosuppressed: congenital or acquired immunodeficiency, SOT, active malignancy receiving chemotherapy, BMT, or autoimmune diseases requiring immunosuppressive therapy, splenectomy, sickle cell disease (auto-splenectomy), Down Syndrome
   f) Pregnancy
7. Pediatric patient 12-17 years old weighing ≥40 kg AND one of the following:
   a) BMI ≥95% for age on CDC growth chart
   b) Immunosuppressed: congenital or acquired immunodeficiency, SOT, active hematologic malignancy receiving chemotherapy, BMT, or autoimmune diseases requiring immunosuppressive therapy
   c) Pregnancy

4. Oral antivirals

The FDA issued Emergency Use Authorization (EUA) for two novel antiviral agents, ritonavir-boosted nirmatrelvir (Paxlovid) and molnupiravir, for the treatment of nonhospitalized adults with mild-to-moderate COVID-19 who are at high risk of progression to severe disease. Key information regarding these therapies is provided below; the full FDA Fact Sheets (molnupiravir) (ritonavir-boosted nirmatrelvir) should be referred to for more details.

**Paxlovid (nirmatrelvir tablet and ritonavir tablets), manufactured by Pfizer, for COVID-19 treatment**

- Paxlovid is an oral drug that has been approved in the U.S. for the treatment of COVID-19.
- The FDA has granted an Emergency Use Authorization (EUA) for use of this drug in adults and adolescents 12 years and older who weigh over 88 lbs (40 kg). with mild-moderate COVID-19 and are at high risk of progression to severe COVID-19 disease.
- Paxlovid should be initiated as soon as possible and must be given within 5 days of symptom onset.
- Paxlovid has significant drug-drug interactions (DDIs). Nirmatrelvir is a substrate of CYP3A, so concomitant administration of strong inducers (i.e., rifampin) may lead to substantial decreases in Paxlovid concentrations, potentially reducing effectiveness. In addition, nirmatrelvir is co-formulated with ritonavir. Ritonavir is a strong CYP3A4 inhibitor and is used to increase the exposure of nirmatrelvir to effective concentrations but
also inhibits the metabolism of many other drugs, potentially leading to toxicities. **Thus, prior to starting a patient on Paxlovid, clinicians should carefully review concomitant medications, including over the counter and herbal products.** The Paxlovid Fact Sheet and the [Liverpool COVID-19 Drug Interactions website](https://www.liverpool.ac.uk/pharmacy/clinical-pharmacy/covid-drug-interactions/) are resources to identify and manage DDIs. Consultation with a pharmacist or infectious diseases specialist may be considered, and in patients receiving specialized therapies (for example, oral chemotherapy), consultation with the appropriate specialist is recommended.

- The usual dose is nirmatrelvir 300 mg (two 150 mg tablets) and ritonavir 100 mg (one 100 mg tablet) orally, with all three tablets taken together, twice daily for 5 days. For patients with eGFR 30-59 mL/min, the dose is 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. eGFR should be calculated using the CKD-EPI equation (online calculator available [here](https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-oral-antiviral-treatment-covid-19)). Paxlovid is not recommended for patients with severe renal impairment (eGFR <30 mL/min) or severe hepatic impairment (Child-Pugh Class C).

**Paxlovid supply and medical treatment**

- The state of Michigan is anticipated to receive a limited supply of Paxlovid the first week of January and will be responsible for allocating inventory.
- Given the scarcity of this drug, Michigan Medicine does not anticipate receiving any supply.
- Greater supply of this drug is anticipated increase in coming months.


**Molnupiravir, manufactured by Merck**

- Molnupiravir is an oral drug that has been approved in the U.S. for the treatment of COVID-19.
- The FDA has granted an Emergency Use Authorization (EUA) of this drug for use in adults 18 years and older with mild-moderate COVID-19 within the first 5 days of symptoms and are at high risk of progression to severe COVID-19 disease, **and for whom alternative COVID-19 treatment options authorized by the FDA are not accessible or clinically appropriate.**
- The dose of molnupiravir is 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days. There are no adjustments for renal and/or hepatic impairment.
- Pages 3 and 4 of the Fact Sheet outline **mandatory requirements** for consideration of molnupiravir and for communication to patients, including discussions regarding use in males of reproductive potential and females of childbearing age and those who are pregnant or breastfeeding.

**Molnupiravir supply and medical treatment**

- The state of Michigan is anticipated to be responsible for allocating inventory.
- Given the scarcity of this drug, Michigan Medicine does not anticipate receiving any supply at this time.
- Check the Michigan Department of Health and Human services website for more information ([https://www.michigan.gov/mdhhs/](https://www.michigan.gov/mdhhs/)).
The recommendations in this guide are meant to serve as treatment guidelines for use at Michigan Medicine facilities. If you are an individual experiencing a medical emergency, call 911 immediately. These guidelines should not replace a provider’s professional medical advice based on clinical judgment, or be used in lieu of an Infectious Diseases consultation when necessary. As a result of ongoing research, practice guidelines may from time to time change. The authors of these guidelines have made all attempts to ensure the accuracy based on current information, however, due to ongoing research, users of these guidelines are strongly encouraged to confirm the information contained within them through an independent source.

If obtained from a source other than med.umich.edu/asp, please visit the webpage for the most up-to-date document.

References:

- http://www.med.umich.edu/i/ice/resources/coronavirus.html

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<tr>
<th>Antimicrobial Subcommittee Approval: N/A</th>
<th>Originated: 03/2020</th>
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<tr>
<td>P&amp;T Approval: N/A</td>
<td>Last Revised: 12/2021</td>
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Revision History:

12/2/20: Added mAb EUA information
12/11/20: Added information on common side effects of mAb therapy
1/8/21: Added mAb eligibility criteria
1/13/21: Added cardiovascular disease criteria
3/15/21: Added bamlanivimab + etesevimab information
4/7/21: Removed bamlanivimab monotherapy reference, adjusted eligibility criteria
6/7/21: Revised mAb criteria and casirivimab + imdevimab hyperlinks
8/10/21: Revised mAb selection and added post-exposure prophylaxis hyperlink.
10/7/21: Revised mAb criteria
10/14/21: Added inhaled corticosteroid section and added sotrovimab
11/12/21: Revised mAb criteria
12/24/21: Removed bamlanivimab + etesevimab & casirivimab + imdevimab, added oral antiviral information