INTERIM
Clinical Guidance on Therapeutics for Outpatient Treatment of COVID-19
(updated January 7, 2022)

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January 7, 2022

Introduction

This clinical guidance was developed through the collaborative efforts of the Healthcare Association of Hawaii (HAH) Hospital Chief Medical Office (CMO) Committee, the HAH CMO sub-group on Clinical Guidance on Therapeutics for Outpatient Treatment of COVID-19, Hawaii's Federally Qualified Health Centers represented by David Derauf, MD, physician subject matter experts, the Hawaii Department of Health, and payor organizations including AlohaCare and Kaiser Permanente.

This is a living document, and will be updated and revised as new treatments become available, as new clinical evidence emerges regarding the efficacy of treatments, and as the COVID pandemic continues to evolve.

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Currently recommended therapeutic agents for outpatient treatment of COVID-19

- Monoclonal antibodies
    - Sotrovimab (EUA)
- Antiviral agents
    - Paxlovid (EUA)
    - Molnupiravir (EUA)
    - Remdesivir (Approved for hospitalized patients. Outpatient use would be off-label indication.)

Patient eligibility for use of therapeutic agents for outpatient treatment of COVID-19

- Patient is:
    - ≥ 12 years of age and ≥ 40kg in weight for Sotrovimab, Remdesivir, and Paxlovid
    - ≥ 18 years of age for Molnupiravir
- Positive results of direct SARS-CoV-2 viral testing
- Mild-to-moderate COVID-19
    - Not hospitalized due to COVID-19, AND
    - Does not require oxygen therapy due to COVID-19 OR does not require an increase in baseline oxygen flow rate due to COVID-19.
- Symptom onset within:
    - 5 days for Molnupiravir and Paxlovid
    - 7 days for Remdesivir
    - 10 days for Sotrovimab
- High risk for progression to severe COVID-19 disease (see Exhibit 1: Medical conditions for high risk progression to severe COVID-19)

Therapeutic agent options for outpatient treatment of COVID-19

- Reference 4. https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-therapies-for-high-risk-nonhospitalized-patients/

- For nonhospitalized patients with mild to moderate COVID-19 who are at high risk of disease progression, it is recommended the following therapeutics are used (listed in order of preference):

    - Nirmatrelvir 300 mg with ritonavir 100 mg (Paxlovid) orally twice daily for 5 days, initiated as soon as possible and within 5 days of symptom onset in those aged ≥12 years and weighing ≥40 kg.

        - Before prescribing ritonavir-boosted nirmatrelvir (Paxlovid), clinicians should carefully review the patient's concomitant medications to evaluate potential significant and complex drug-drug interactions.

        - Reference 5. https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-paxlovid-drug-drug-interactions/

    - Sotrovimab 500 mg as a single IV infusion, administered as soon as possible and within 10 days of symptom onset in those aged ≥12 years and weighing ≥40 kg who live in areas with a high prevalence of the Omicron VOC.

        - If the Delta VOC still represents a significant proportion of infections in the region and other options are not available or are contraindicated, patients can be offered bamlanivimab plus etesevimab or casirivimab plus imdevimab, with the understanding that this treatment would be ineffective if they are infected with the Omicron VOC.

    - Remdesivir 200 mg IV on Day 1, followed by remdesivir 100 mg IV daily on Days 2 and 3, initiated as soon as possible and within 7 days of symptom onset in those aged ≥12 years and weighing ≥40 kg.

        - Remdesivir is currently approved by the FDA for use in hospitalized individuals, and outpatient treatment would be an off-label indication.

    - Molnupiravir 800 mg orally twice daily for 5 days, initiated as soon as possible and within 5 days of symptom onset in those aged ≥18 years ONLY when none of the above options can be used.

        - The FDA EUA states that molnupiravir is not recommended for use in pregnant patients due to concerns about the instances of fetal toxicity observed during animal studies. However, when other therapies are not available, pregnant people with COVID-19 who are at high risk of progressing to severe disease may reasonably choose molnupiravir therapy after being fully informed of the risks, particularly those who are beyond the time of embryogenesis (i.e., >10 weeks' gestation). The prescribing clinician should document that a discussion of the risks and benefits occurred and that the patient chose this therapy.

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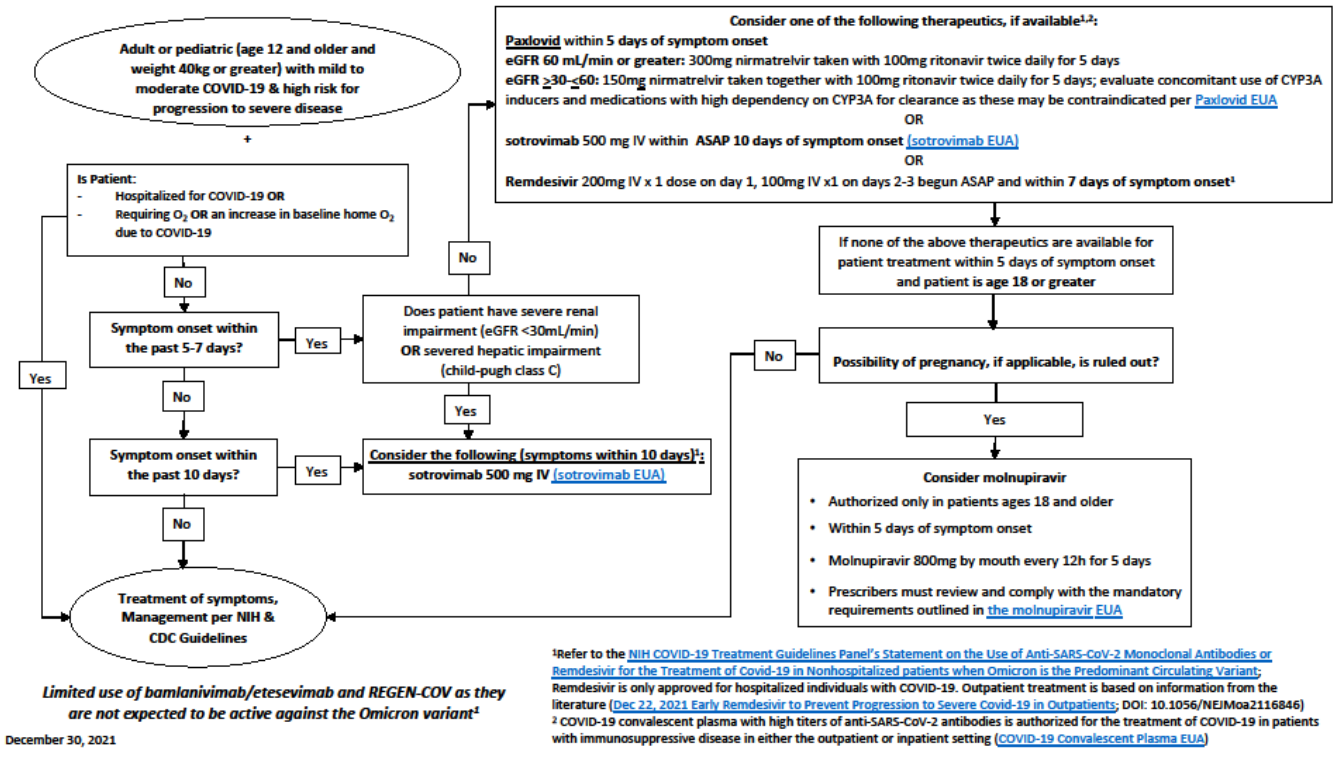
Outpatient COVID-19 Therapeutics Treatment Aid Algorithm

- Reference 6. https://www.phe.gov/emergency/events/COVID19/therapeutics/Documents/COVID-Therapeutics-Decision-Aid.pdf



Prioritization of patients at highest risk of progression to severe COVID-19

- It is anticipated there may be limitations that make it difficult to provide therapeutic agents to all who are at high risk of progression to severe COVID-19 and might benefit from these therapies.
- When constraints limit the availability of therapeutic agents, it is recommended that the Risk Group Tiers (below) be used to prioritize patients at highest risk of clinical progression for use of therapeutic agents. The groups are listed by tier in descending order of priority.
- See Exhibit 2: CDC Definition of Fully Vaccinated
- Reference 7. https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-patient-prioritization-for-outpatient-therapies/

Tier	Risk Group
1	• Immunocompromised individuals not expected to mount an adequate immune response to COVID-19 vaccination or SARS-CoV-2 infection due to their underlying conditions, regardless of vaccine status (see Exhibit 3: Immunocompromising Conditions); or • Unvaccinated individuals at the highest risk of severe disease (anyone aged ≥75 years or anyone aged ≥65 years with clinical risk factors).
2	• Unvaccinated individuals at risk of severe disease not included in Tier 1 (anyone aged ≥65 years or anyone aged <65 years with clinical risk factors)
3	• Vaccinated individuals at high risk of severe disease (anyone aged ≥75 years or anyone aged ≥65 years with clinical risk factors) Note: Vaccinated individuals who have not received a COVID-19 vaccine booster dose are likely at higher risk for severe disease; patients in this situation within this tier should be prioritized for treatment.
4	• Vaccinated individuals at risk of severe disease (anyone aged ≥65 years or anyone aged <65 with clinical risk factors) Note: Vaccinated individuals who have not received a COVID-19 vaccine booster dose are likely at higher risk for severe disease; patients in this situation within this tier should be prioritized for treatment.

References

1. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of sotrovimab. November 2021. Available at: https://www.fda.gov/media/149534/download
2. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of paxlovid. December 2021. Available at: https://www.fda.gov/media/155050/download
3. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of molnupiravir. 2021. Available at: https://www.fda.gov/media/155054/download
4. National Institute of Health. COVID-19 Treatment Guidelines: Panel's statement on therapies for high-risk, nonhospitalized patients with mild to moderate COVID-19. https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-therapies-for-high-risk-nonhospitalized-patients/. Accessed on January 3, 2022.
5. National Institute of Health. COVID-19 Treatment Guidelines: Panel's statement on potential drug-drug interactions between ritonavir-boosted nirmatrelvir (paxolovid) and concomitant medications. https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-paxlovid-drug-drug-interactions/. Accessed on January 7, 2022.
6. Department of Health and Human Services. Office of the Assistant Secretary for Preparedness and Response. Public Health Emergency. Therapeutics Document: Covid Therapeutics Decision Aid. https://www.phe.gov/emergency/events/COVID19/therapeutics/Documents/COVID-Therapeutics-Decision-Aid.pdf. Accessed on January 7, 2022.
7. National Institute of Health. COVID-19 Treatment Guidelines: Panel's interim statement on patient prioritization for outpatient anti-SARS-CoV-2 therapies or preventative strategies when there are logistical or supply constraints. https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-patient-prioritization-for-outpatient-therapies/. Accessed on January 3, 2022.

Exhibit 1

Medical conditions for high risk progression to severe COVID-19

The following medical conditions or other factors may place adults and pediatric patients (12 to 17 years of age weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example ≥65 years of age)
- Obesity or being overweight (for example, adults with BMI >25 kg/m2, or if 12 to 17 years of age, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm)
- Pregnancy
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension)
- Sickle cell disease
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation [not related to COVID 19])

Other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19. For additional information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the CDC website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

Exhibit 2
CDC Definition of Fully Vaccinated

Individuals are considered fully vaccinated against COVID-19 if they have received a primary series of a COVID-19 vaccine. A primary series consists of:

- A 2-dose series of an mRNA COVID-19 vaccine (Pfizer-BioNTech or Moderna), OR
- A single-dose COVID-19 vaccine (Johnson & Johnson's Janssen vaccine)

Exhibit 3
Immunocompromising Conditions

If these COVID-19 therapeutic agents cannot be provided to all moderately to severely immunocompromised individuals because of logistical constraints or supply limitations, it is recommended their use for those who are least likely to mount an adequate response to COVID-19 vaccination or SARS-CoV-2 infection and who are at risk for severe outcomes, including (but not limited to) the following patients:

- Patients who are within 1 year of receiving B-cell depleting therapies (e.g., rituximab, ocrelizumab, ofatumumab, alemtuzumab)
- Patients receiving Bruton tyrosine kinase inhibitors
- Chimeric antigen receptor T cell recipients
- Post-hematopoietic cell transplant recipients who have chronic graft versus host disease or who are taking immunosuppressive medications for another indication
- Patients with hematologic malignancies who are on active therapy
- Lung transplant recipients
- Patients who are within 1 year of receiving a solid-organ transplant (other than lung transplant)
- Solid-organ transplant recipients with recent treatment for acute rejection with T or B cell depleting agents
- Patients with severe combined immunodeficiencies
- Patients with untreated HIV who have a CD4 T lymphocyte cell count <50 cells/mm^3

If supplies are extremely limited, it is recommended prioritizing those who are more severely immunocompromised (see above list) and who also have additional risk factors for severe disease (see Exhibit 1: Medical conditions for high risk progression to severe COVID-19) for the outpatient therapies.