COVID Therapeutic Guidance

December 2021

NIH Patient Prioritization for Treatment when Constraints are Present

Tier	Risk Group
1	• Any *unvaccinated* person ≥75 years • Any *unvaccinated* person ≥65 years with additional risk factors (1) • *Immunocompromised* individuals not expected to mount an adequate immune response to COVID-19 vaccination or SARS-CoV-2 infection due to underlying conditions, *regardless of vaccine status* (2)
2	• Any *unvaccinated* individuals ≥65 years • Any *unvaccinated* patient <65 years with clinical risk factors (1)
3	• Any vaccinated person ≥75 years • Any vaccinated person ≥65 years with clinical risk factors (1) 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	• Any vaccinated person ≥65 years • Any vaccinated person <65 with clinical risk factors (1) 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.

1. Underlying Conditions:
Obesity or being overweight (BMI >25 kg/m2 or if age 12-17 with BMI ≥85th percentile for age and gender), Pregnancy, Chronic kidney disease, Diabetes, Immunosuppressive disease or immunosuppressive treatment, Cardiovascular disease (including congenital heart disease) or hypertension, Chronic lung diseases (e.g., COPD, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis, and pulmonary hypertension), Sickle cell disease, Neurodevelopmental disorders (e.g., cerebral palsy) or other conditions that confer medical complexity (e.g., 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)), At risk racial or ethnic group.
2. Immunocompromised Conditions:
Patients within 1 year of receiving B-cell depleting therapies (e.g., rituximab, ocrelizumab, ofatumumab, alemtuzumab), receiving Bruton tyrosine kinase inhibitors, CAR-T cell recipients, post-hematopoietic cell transplant recipients who have chronic graft versus host disease or who are taking immunosuppressive medications for another indication, hematologic malignancies on active therapy, lung transplant recipients, 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, severe combined immunodeficiencies, untreated HIV with a CD4 cell count <50 cells/mm3

NIH Recommended Order of Preference: Paxlovid, Sotrovimab, Remdesivir then Molnupiravir (Appendix A). **Fluvoxamine** is **not** currently recommended for treatment of COVID-19 by NIH guidelines, IDSA guidelines, or endorsed by Legacy Infectious Diseases due to lack of high-quality evidence for benefit and potential for side effects.

	Nirmatrelvir/ritonavir (Paxlovid)	Sotrovimab (Xevudy)	Molnupiravir (Lageviro)
Authorized for	High-risk* outpatients ≥ 12 years of age weighing at least 40kg with mild-moderate COVID-19. **Patient Inclusion Criteria:** • Laboratory confirmed COVID-19 • Symptom onset ≤ 5 days • Unvaccinated for COVID-19** **Patient Exclusion Criteria:** • eGFR < 30 mL/min or ESRD • Severe hepatic impairment • Known (HIV) infection with a viral load greater than 400 copies/mL • Use of strong CYP3A4 substrates/inducers (see Appendix B) • Suspected or confirmed concurrent active systemic infection other than COVID-19 • SpO2 ≤ 94% ***High risk**: age > 60 years, diabetes, BMI >25, chronic lung disease (including asthma), chronic kidney disease, current smoker, immunosuppressive disease or treatment, cardiovascular disease, hypertension, sickle cell disease, neurodevelopmental disorders, active cancer, medically related technological dependence	High-risk* outpatients ≥ 12 years of age weighing at least 40kg with mild-moderate COVID-19. **Patient Inclusion Criteria:** • Laboratory confirmed COVID-19 • Symptom onset ≤ 10 days **Patient Exclusion Criteria:** • Current hospitalization for COVID-19 • Previous serious hypersensitivity to another monoclonal antibody • SpO2 ≤ 94% ***High risk**: older age (>65 years of age), obesity (BMI ≥25), pregnancy, chronic kidney disease, diabetes, immunosuppressive disease or treatment, cardiovascular disease, chronic lung disease, sickle cell disease, neurodevelopmental disorders, medical-related technological dependence	High-risk* outpatients ≥ 18 years of age with mild-to-moderate COVID-19. **Patient Inclusion Criteria:** • Laboratory confirmed COVID-19 • Symptom onset ≤ 5 days • Unvaccinated for COVID-19** • **When other options are not available or cannot be used****** **Patient Exclusion Criteria:** • eGFR < 30 mL/min or ESRD • LFTs > 3x ULN • HIV w/ viral load > 50 copies/mL • Pregnancy or breastfeeding • Severe neutropenia (absolute neutrophil count of <500/mL) • Platelet count <100,000/mcL • SpO2 ≤ 94% ***High risk**: over 60 years of age, diabetes, obesity (BMI ≥30), chronic kidney disease, serious heart conditions, chronic obstructive pulmonary disease, or active cancer

Prepared by: Tiffany Wu, PharmD, PGY2 ID Resident & Emily Shephard, PharmD
Reviewed by: Eric Chang, MD & Regina Won, MD
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	Nirmatrelvir/ritonavir (Paxlovid)	Sotrovimab (Xevudy)	Molnupiravir (Lageviro)
Not Authorized for	• Treatment of COVID in hospitalized patients • Pre-exposure or post-exposure prophylaxis • Usage > 5 days	• Treatment of COVID in hospitalized patients • Treatment of patients who require oxygen therapy due to COVID • Treatment of patients who require an increase baseline oxygen flow rate due to COVID	• Treatment of COVID in hospitalized patients • Pre-exposure or post-exposure prophylaxis • Usage > 5 days • Patients <18 years of age
Dose	Nirmatrelvir 300mg + ritonavir 100mg twice daily by mouth for 5 days. Take with or without food. **Dose reduction in eGFR ≥30 to <60 ml/min**: 150 mg nirmatrelvir + 100mg ritonavir twice daily for 5 days. Take with or without food.	Sotrovimab 500 mg IV infusion over 30 minutes x1 dose. **Patients must be monitored for at least 1 hour following administration.**	Molnupiravir 800 mg by mouth every 12 hours for 5 days. Take with or without food.
Safety	**Warning**: • Serious drug-drug interactions with CYP3A4 substrates/inducers • Hepatotoxicity • Risk of HIV-1 drug resistance **Common adverse effects**: dysgeusia, diarrhea, hypertension, myalgia	**Warning**: • Hypersensitivity reactions • Clinical worsening of COVID-19 has been seen following administration of monoclonal antibodies **Common adverse effects**: rash, diarrhea	**Warning**: • Embryo-fetal toxicity: Not recommended for use during pregnancy • Bone and Cartilage Toxicity: Not for <18 years of age or breastfeeding **Common adverse effects**: diarrhea, nausea, dizziness
Special Considerations	• Pregnancy or breastfeeding*** • Mix-and-match of outpatient COVID-19 therapeutics is not currently recommended	• Pregnancy or breastfeeding*** • Mix-and-match of outpatient COVID-19 therapeutics is not currently recommended	• Use caution in individuals of childbearing potential (counsel females to use appropriate contraceptives during treatment and for 4 days following treatment and males with partners of childbearing potential should be advised to use effective contraception during treatment and for 3 months following treatment with molnupiravir) • Breastfeeding is not recommended during treatment and 4 days following treatment with molnupiravir. • Mix-and-match of outpatient COVID-19 therapeutics is not currently recommended

** Benefit of Paxlovid and Molnupiravir is unknown in vaccinated or previously infected patients.

*** Safety and efficacy data in pregnant and lactating women is lacking but the Society for Maternal-Fetal Medicine supports the use of Paxlovid in pregnant women with COVID-19 who meet clinical qualifications.

**** Given lower efficacy Molnupiravir should only be used when other options are not available HAN Archive - 00461 | Health Alert Network (HAN) (cdc.gov) and Statement on Therapies for High-Risk, Nonhospitalized Patients | COVID-19 Treatment Guidelines (nih.gov)

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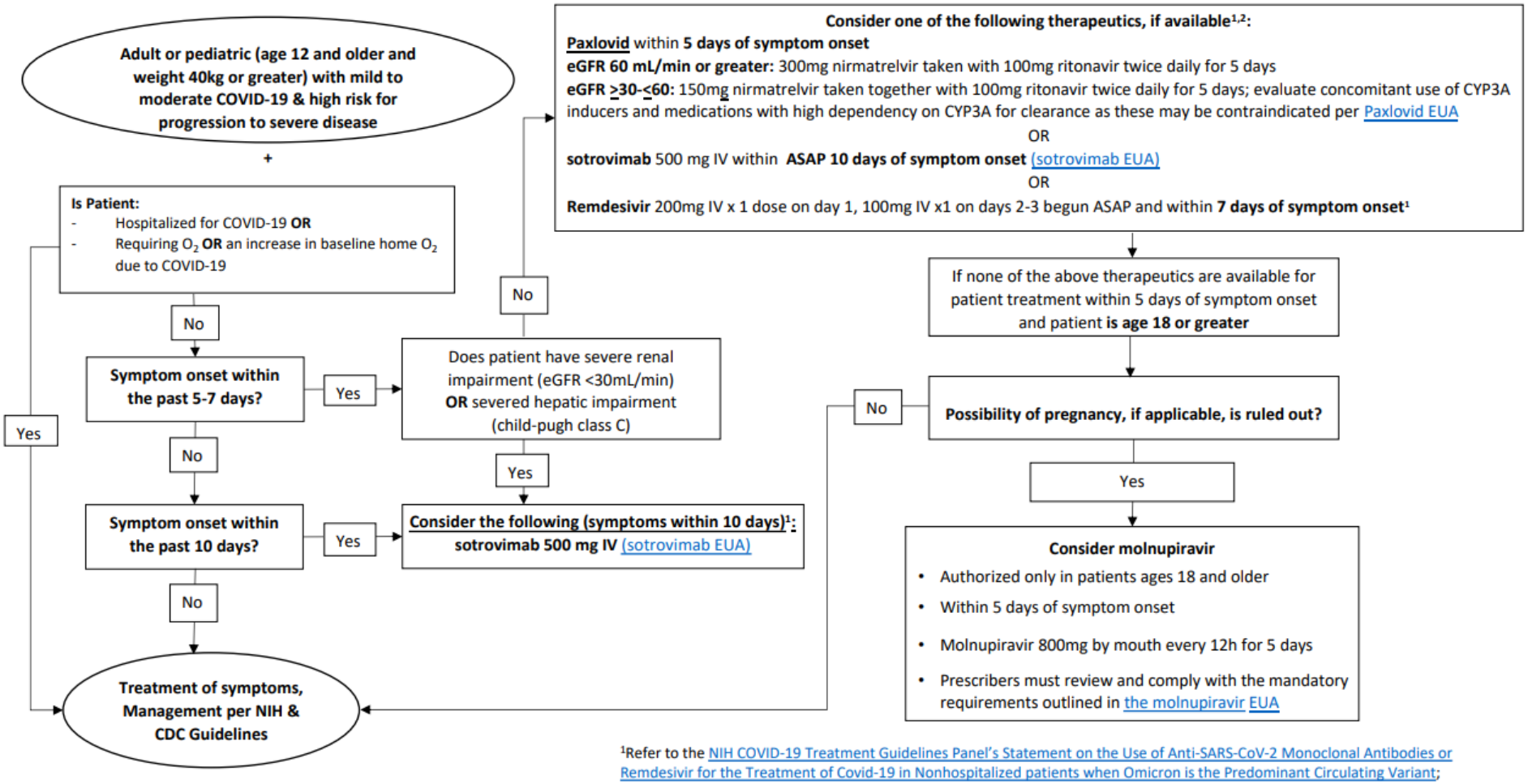
Appendix A. HHS Suggested Algorithm for Selecting a Treatment Option



Limited use of bamlanivimab/etesevimab and REGEN-COV as they are not expected to be active against the Omicron variant[1]

December 30, 2021

[1]Refer to the NIH COVID-19 Treatment Guidelines Panel's Statement on the Use of Anti-SARS-CoV-2 Monoclonal Antibodies or Remdesivir for the Treatment of Covid-19 in Nonhospitalized patients when Omicron is the Predominant Circulating Variant; Remdesivir is only approved for hospitalized individuals with COVID-19. Outpatient treatment is based on information from the literature (Dec 22, 2021 Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients; DOI: 10.1056/NEJMoa2116846)

[2] COVID-19 convalescent plasma with high titers of anti-SARS-CoV-2 antibodies is authorized for the treatment of COVID-19 in patients with immunosuppressive disease in either the outpatient or inpatient setting (COVID-19 Convalescent Plasma EUA)

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Appendix B. Paxlovid Drug Interactions

Recommended to use an appropriate drug-drug interaction checker prior to Paxlovid prescribing: Liverpool COVID-19 Interactions (covid19-druginteractions.org)

Do not use Paxlovid if patient is receiving any of the following medications	If the patient is receiving any medications listed • Withhold the medication for the duration of Paxlovid treatment if appropriate, or • Do not use Paxlovid
• Amiodarone • Apalutamide • Bosentan • Carbamazepine • Cisapride • Clopidogrel • Clozapine • Colchicine in patients with renal and/or hepatic impairment • Disopyramide • Dofetilide • Dronedarone • Eplerenone • Ergot derivatives • Flecainide • Flibanserin • Glecaprevir/pibrentasvir • Ivabradine • Lumateperone • Lurasidone • Mexiletine • Phenobarbital • Phenytoin • Pimozide • Propafenone • Quinidine • Ranolazine • Rifampin • Rifapentine • Rivaroxaban • Sildenafil for pulmonary hypertension • St. John's wort • Tadalafil for pulmonary hypertension • Ticagrelor • Vorapaxar	• Alfuzosin • Alprazolam • Atorvastatin • Avanafil • Clonazepam • Codeine • Cyclosporine* • Diazepam • Everolimus* • Fentanyl • Hydrocodone • Lomitapide • Lovastatin • Meperidine (pethidine) • Midazolam (oral) • Oxycodone • Piroxicam • Propoxyphene • Rosuvastatin • Salmeterol • Sildenafil for erectile dysfunction • Silodosin • Simvastatin • Sirolimus* • Suvorexant • Tacrolimus* • Tadalafil for erectile dysfunction • Tamsulosin • Tramadol • Triazolam • Vardenafil *Do not hold medication or prescribe Paxlovid without consulting the patient's specialist provider due to potential need for therapeutic drug monitoring

Table adapted from: NIH COVID Guidelines. Available at: COVID-19 Treatment Guidelines (nih.gov)

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