**Update on Medications to Treat Mild/Moderate COVID Infection**

* Due to increase in the proportion of cases caused by the Omicron BA.2 subvariant, the monoclonal antibody sotrovimab is no longer authorized to treat COVID-19 infections.
* Bebtelovimab is *effective* against the Omicron BA.2 subvariant and is available at Lurie for treatment of mild/moderate COVID infection *for patients* ≥ 12 years and ≥ 40 kg.
* Nirmatrelvir/ritonavir (Paxlovid), an oral anti-viral medication, is also availableand is authorized for patients ≥12 years and ≥ 40 kg.
* **Currently, there is adequate supply of COVID therapeutics.** If supply becomes limited, priority will be given to patients who are very high risk for progression to severe COVID-19 infection.
* **For both Lurie and Lurie Network Providers please use this HIPAA compliant form to submit a request for COVID-19 medications for children with high-risk conditions who are not currently hospitalized.**

<https://lurieoncology.iad1.qualtrics.com/jfe/form/SV_8nNeYHdSK6kL6qG>

* **For additional guidance please see the accompanying flow sheet, including descriptions of eligibility criteria (Appendix A), prioritization tiers (Appendix B), and a medication information (Appendix C).**

*Additional Information*

* New CDC guidance states that if mAbs are administered, a waiting period is no longer required prior to the next COVID vaccine dose.
* For guidance on hospitalized patients please contact the Transplant ID service.
* Please note that currently there are no mAbs or oral antivirals authorized for patients < 12 years for <40 kg. This form may also be used to submit information for consideration of short course remdesivir therapy for younger children who are high risk.
* For additional questions, please contact Sameer Patel (sjpatel@luriechildrens.org, office/pager 74667) or the Infectious Diseases office (312-227-4080) for additional questions.

*This guideline will be updated as additional medication supply and public health guidance are made available.*

ID Service will place order and coordinate dispense with patient/family.

No

Complete Outpatient COVID Therapeutic Request Form by 2PM

<https://lurieoncology.iad1.qualtrics.com/jfe/form/SV_8nNeYHdSK6kL6qG> **OR**

ED may dispense Nirmatrelvir/Ritonavir after discussion with ID Service.

ID Service/Pharmacy to allocate therapy for next day based on availability, priority (Appendix B), and medical contraindications. Will communicate availability with requesting provider.

Oral Antivirals

Monoclonal Ab

No Allocation

Yes

Yes

Patient/Family Information Sheets:

*English*

[Bebtelovimab](https://www.fda.gov/media/156153/download)

[Nirmatrelvir/ritonavir](http://labeling.pfizer.com/ShowLabeling.aspx?id=16473)

[Molnupiravir](https://www.fda.gov/media/155055/download)

[Remdesivir](https://doh.sd.gov/documents/COVID19/Remdesivir_EUA_FactSheet_ParentsCaregivers.pdf)

*Spanish*

[Bebtelovimab](https://www.fda.gov/media/156155/download)

[Nirmatrelvir/ritonavir](https://www.fda.gov/media/155075/download)

[Molnupiravir](https://www.fda.gov/media/155115/download)

[Remdesivir](https://www.gilead.com/-/media/files/pdfs/remdesivir/eua-fact-sheet-for-patients-and-caregivers_spanish-language.pdf)

Description of Anti-Viral Therapy for COVID-19

(Appendix C)

Hospital Admission

Remdesivir plus Dexamethasone

Consider second immunomodulatory drug

Resp Distress or Increase 02 Requirement?

**Additional Points:**

* Currently we are not offering mAb for post-exposure prophylaxis.
* Patients who are vaccinated and have breakthrough symptomatic disease can receive mAb if they meet the eligibility criteria.
* Combination therapy with antivirals and monoclonal Ab is not recommended at this time.
* If due for COVID vaccine, a waiting period after monoclonal Ab administration is no longer required.
* Duration of isolation is not modified by receipt of mAb or receipt of antivirals.

No

Supportive Care

Positive COVID Test (PCR or Antigen)

Mild/Moderate Illness

>12 y and

>40 kg?

Eligible for Therapeutics

Appendix A?

If no mAb or oral antivirals available

Automatically considered for reallocation the next day depending on risk status and duration of illness.

This guideline is for patients with COVID infection.

For prevention of infection in immunocompromised patients please refer to guidelines for pre-exposure prophylaxis with

Tixagevimab/Cilgavimab (EvuSheld)

ID Service or requesting provider places AIC infusion request for mAb OR inpatient bed request if no AIC slot available.

Asymptomatic

Monitor

Discus with ID if Priority Tier 1 (Appendix B)

Supportive Care

Discuss with ID if Priority Tier 1 (Appendix B) to determine if candidate for Remdesivir

Flowchart for Management of Patients with Mild/Moderate COVID Infection

**Appendix A: Eligibility**

Patients are eligible if they have of the following clinical presentations AND have an eligible risk factor for progression to severe disease.

Clinical Presentations

* Non-hospitalized children ≥12 years with mild to moderate illness
* Hospitalized children of all ages with mild to moderate illness if reason for admission or continued hospitalization is for concurrent management of chronic conditions\*
* Asymptomatic children who test positive for COVID\*\*

*\*Note that patients who require ventilatory/oxygen support over baseline are not eligible.*

*\*\*ID service will assess asymptomatic children with positive COVID test for high risk of progression for COVID disease based on chronic condition and date of exposure.*

Risk Factor

* **Neuromuscular or neurological disease with respiratory compromise**
* **Chronic lung disease, including ventilated patients and those on baseline supplemental 02**
* **Sickle cell disease and thalassemia**
* **Congenital or acquired heart disease1**
* **High risk asthma2**
* **Obesity (BMI> 95th percentile) in children ≥8 years**
* **Genetic or metabolic syndromes**
* **Severe congenital anomalies**
* **An immunocompromising condition or immunosuppressive treatment3**

1typically includes, but is not limited to, palliated single ventricle/Fontan, chronic cardiac cyanosis (<85%), cardiac dysfunction requiring anti-congestive medications, significant cardiomyopathy requiring medications, pulmonary hypertension, heart transplant.

2hospitalization in the ICU in the last 12 months for status asthmaticus; 2 or more hospitalizations in the last 12 months for status asthmaticus, patients on maximal therapy (mid to high dose inhaled corticoid steroids plus second controller) who require systemic steroids.

3will be decided on a case-by-case basis due based on degree of immune compromise.

**Appendix B. Priority Tiers for Treatment of COVID Monoclonal Ab**

* Tier 1: Patients with one or more of the following conditions:
	+ Stem cell transplantation OR CAR-T treatment OR receipt of B-cell depleting agents in the prior 6 months OR receiving immune suppression for GVHD
	+ Receipt of solid organ transplant OR treatment of rejection in the prior 6 months
	+ Known or suspected primary immunodeficiency (per immunology), including agammaglobulinemia, T cell lymphopenia, requirement of IVIG replacement or antimicrobial prophylaxis
	+ Chronic lung disease requiring oxygen OR severe restrictive lung disease including caused by congenital abnormalities or muscular dystrophy
	+ Moderately to severely depressed cardiac function OR single ventricle physiology OR complex congenital heart disease, cardiomyopathy or pulmonary HTN requiring heart failure or pulmonary hypertension treatment (medication or mechanical support)
	+ Sickle cell disease with 2 or more hospitalizations for pain and/or acute chest syndrome in the last 12 months
	+ Obesity BMI >99 %ile
* Tier 2: Patients not in Tier 1 with ≥2 risk factors for progression to severe disease (see Appendix A).
* Tier 3: Patients with one risk factor for progression to severe disease (see Appendix A).

Vaccination of patients and family members is strongly recommended to reduce household and community infection, and risk of re-infection.

**Appendix C: Description of Anti-Viral Therapy for COVID-19 Infection**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Remdesivir** **(RDV, Veklury®)1** | **Sotrovimab3****Currently Suspended** | **Bebtelovimab4** | **Nirmatrelvir/ritonavir (Paxlovid™)5** | **Molnupiravir6** |
| **Indication** | Mild-moderate COVID-19Severe COVID-19 | Mild-moderate COVID-19 | Mild-moderate COVID-19 | Mild-moderate COVID-19 | Mild-moderate COVID-19 |
| **Age/weight****eligibility** | All ages and ≥ 3.5kg | ≥ 12 years and ≥ 40 kg | ≥ 12 years and ≥ 40 kg | ≥ 12 years and ≥ 40 kg | ≥ 18 years  |
| **Pediatric clinical trial information** | A randomized clinical trial evaluated the efficacy and safety of a 3-day course of RDV among high-risk, non-hospitalized patients diagnosed with COVID-19,2 and resulted in an 87% lower risk of hospitalization or death than placebo by Day 28.Eight patients younger than 18 years of age were included in the trial: n=3 in remdesivir group and, n=5 in placebo group.  | Safety and effectiveness of sotrovimab have not been assessed in pediatric patients. Recommended dosing regimen in patients 12 years to less than 18 years of age, weighing at least 40kg, is expected to result in comparable serum exposures of sotrovimab as those observed in adults based on an allometric scaling approach.The COMET-ICE trial enrolled adult patients assigned to sotrovimab (n=291) vs. placebo (n=292) with mild to moderate COVID-19 who were at high risk for progression to severe disease. Use of sotrovimab was associated with a 6% absolute reduction and an 85% relative reduction in hospitalizations or death.  | Safety and effectiveness of bebtelovimab have not been assessed in pediatric patients. Recommended dosing regimen in patients 12 years to less than 18 years of age, weighing at least 40kg, is expected to result in comparable serum exposures of bebtelovimab as those observed in adults. | The pharmacokinetics of nirmatrelvir/ritonavir in patients < 18 years of age have not been evaluated. Using a population pharmacokinetic model, dosing regimen is expected to result in comparable steady-state plasma exposure of nirmatrelvir in patients 12 years of age and older and weighing at least 40 kg to those observed in adults after adjusting for body weight.  | Not authorized in patients <18 years of age because it may affect bone and cartilage growth. Safety and efficacy of molnupiravir have not been established in pediatric patients.  |
| **Mechanism of action**  | Binds to RNA-dependent RNA polymerase and acts as an RNA-chain terminator | Monoclonal antibody that targets epitope in the receptor-binding domain of the spike protein that is conserved between SARS-CoV and SARS-CoV-2. Inhibits an undefined step that occurs after virus attachment and prior to fusion of the viral and cell membranes.  | Recombinant human IgG1-kappa monoclonal antibody that binds to a conserved epitope on the spike protein receptor binding domain of SARS-CoV-2. Bebtelovimab binds to the spike protein and blocks spike protein attachment.  | Nirmatrelvir is a SARS-CoV-2 main protease inhibitor, preventing viral replication. Ritonavir is an HIV-1 protease inhibitor and CYP3A inhibitor but is not active against SARS-CoV-2. Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, resulting in increased plasma concentrations of nirmatrelvir. | Inhibits SARS-CoV-2 replication by viral mutagenesis |
| **Route of administration**  | Intravenous | Intravenous | Intravenous | Oral | Oral |
| **Dose and duration** | Based on age/weight: **< 12 years of age and weight between 3.5-40kg:** 5 mg/kg on Day 1 (max dose: 200mg), followed by 2.5 mg/kg daily (max dose: 100mg). The powder formulation should be used. **<12 years of age and weight > 40kg:** 200mg (loading dose) on Day 1, followed by 100mg IV daily. **≥12 years of age and weight < 40 kg:** 5 mg/kg on Day 1 (max dose: 200mg), followed by 2.5 mg/kg (max dose: 100mg) daily. **≥12 years of age and weight ≥ 40kg:** 200mg (loading dose) on Day1 and 100mg IV daily. Duration: *Mild/moderate disease*: 3 days*Severe Disease*Patients not requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO): 5 days. Therapy may be extended for up to 5 additional days for a total treatment duration of up to 10 days if a patient does not demonstrate clinical improvement. Patients requiring invasive mechanical ventilation and/or ECMO: 10 days Renal impairment: Safety and efficacy of RDV has not been assessed in patients with severe renal impairment. RDV is not recommended in patients with GFR < 30mL/min or in full-term neonates with serum creatinine ≥ 1mg/dL unless potential benefit outweighs potential risk. Hepatic impairment: It is unknown if dose adjustments are required in patient with hepatic impairment. RDV should be used in patients with hepatic impairment if the potential benefit outweighs the risk. RDV should not be initiated in patients with ALT ≥5 times the upper limit of normal at baseline. | Sotrovimab 500mg IV is administered over 30 minutes.No dosage adjustment is recommended based on renal impairment, during pregnancy or while lactating. No clinical trials have been conducted to evaluate the effects of hepatic impairment on the pharmacokinetic of sotrovimab.  | Bebtelovimab 175mg IV administered over at least 30 secondsNo dosage adjustment is recommended in individuals with renal impairment or in individuals with mild hepatic impairment. | Nirmatrelvir 300mg (two 150 mg tablets) with ritonavir 100mg (one 100mg tablet), with all three tablets taken together twice daily for 5 days. Nirmatrelvir must be co-administered with ritonavir. Prescriptions should specific the numeric dose of each active ingredient within nirmatrelvir-ritonavir. Dose adjustment is required for moderate renal impairment (eGFR ≥30 to < 60 mL/min): Nirmatrelvir 150mg (one 150 mg tablet) with ritonavir 100mg (one 100mg tablet), with both tablets taken together twice daily for 5 days. Nirmatrelvir must be co-administered with ritonavir.Nirmatrelvir-ritonavir is not recommended in patients with severe renal (eGFR <30 mL/min) or hepatic impairment (Child-Pugh Class C).  | Molnupiravir 800mg (four 200mg capsules) taken orally every 12 hours for 5 days.No dosage adjustment is recommended based on renal or hepatic impairment.  |
| **Contra-indications/****Warnings** | Contraindication:History of clinically significant hypersensitivity reactions to RDV or any components of the product. Warnings: Hypersensitivity, including anaphylaxis and infusion-related reactions. Slower infusion rates, with a maximum infusion time of up to 120 minutes, can be considered to potentially prevent these signs and symptoms. Increased risk of transaminase elevations. RDV should be discontinued in patients who develop: • ALT ≥10 times the upper limit of normal during treatment• ALT elevation accompanied by signs or symptoms of liver inflammation | Contraindication: History of anaphylaxis to sotrovimab or to any of the excipients in the formulation Warnings:Hypersensitivity, including anaphylaxis and infusion-related reactions. Consider slowing or stopping infusion and administer appropriate medications and/or supportive care if an infusion-related reaction occurs. Clinical worsening of COVID-19 after administration of SARS-CoV-2 monoclonal antibody treatment has been reported.  | Contraindication: No contraindications have been identified based on the limited available data.Warnings:Hypersensitivity, including anaphylaxis and infusion-related reactions. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care. Administer appropriate medications and/or supportive care if an infusion-related reaction occurs. Clinical worsening of COVID-19 after administration of SARS-CoV-2 monoclonal antibody treatment has been reported.  | Contraindication: History of clinically significant hypersensitivity reactions to active ingredients or any other components of the product. Contraindicated with medication that are highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions. Contraindicated with medications that are potent CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virological response and possible resistant. Review list of clinically significant drug interactions, including contraindicated medications within clinical drug resources (e.g., Lexi-Comp, Micromedex) for comprehensive information.  | Contraindication: No contraindications have been identified based on the limited available data.Warnings: Based on animal studies, molnupiravir may cause fetal harm when administered to pregnant individuals. There are no available human data on the use of molnupiravir in pregnant individuals to evaluate risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Therefore, molnupiravir is not recommended for use during pregnancy. Molnupiravir is authorized to be prescribed to a pregnant individual only after the healthcare provider has determined that the benefits outweigh the risks for that individual patient. There is a pregnancy surveillance program that monitors pregnancy outcomes in individuals exposed to molnupiravir during pregnancy.Prior to initiating treatment with molnupiravir, assess whether an individual of childbearing potential is pregnant or not, if clinically indicated. Pregnancy status does not need to be confirmed in patients who have undergone permanent sterilization, are currently using and intrauterine system or contraceptive implant, or in whom pregnancy is not possible.Females of childbearing potential should use a reliable method of contraception for the duration of treatment and for 4 days after the last dose of molnupiravir. Males of reproductive potential who are sexually active with females of childbearing potential should use a reliable method of contraception during treatment and for at least 3 months after the last dose. |
| **Drug interactions**  | Hydroxychloroquine and chloroquine may diminish the effects of RDV. Based on *in vitro* data, chloroquine has an antagonistic effect on the intracellular metabolic activation and antiviral activity of RDV. Concomitant use of RDV with chloroquine or hydroxychloroquine is not recommended. Review list of drug-drug interactions within clinical drug resources (e.g., Lexi-Comp, Micromedex) for comprehensive information. | Drug-drug interaction studies have not been performed with sotrovimab. Sotrovimab is not renally excreted or metabolized by CYP enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of CYP enzymes are unlikely.  | None documented. Bebtelovimab is not renally excreted or metabolized by cytochrome P450 (CYP) enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of CYP enzymes are unlikely. | Concomitant use of nirmatrelvir-ritonavir and certain other drugs may result in potentially significant drug interactions. Consider the potential for drug interactions prior to and during nirmatrelvir-ritonavir therapy. Review list of drug-drug interactions within clinical drug resources (e.g., Lexi-Comp, Micromedex) for comprehensive information. | Cladribine |
| **Adverse effects** | Nausea, increased AST, increased ALT, hypersensitivity reactions, generalized seizure, rash, administration site extravasation Prescribing healthcare provider and/or provider’s designee are/is responsible for mandatory reporting of all serious adverse events\* and medication errors potentially related to RDV within 7 calendar days from the onset of the event, using FDA form 3500. Please review the fact sheet for healthcare providers: EUA of RDV for instructions on how to submit adverse event reports to FDA MedWatch. | Clinical trials evaluating safety of sotrovimab are ongoing. Prescribing healthcare provider and/or provider’s designee are/is responsible for mandatory reporting of all serious adverse events\* and medication errors potentially related to sotrovimab within 7 calendar days from the onset of the event, using FDA form 3500. Please review the fact sheet for healthcare providers: EUA of sotrovimab for instructions on how to submit adverse event reports to FDA MedWatch. | Infusion-related reactions, pruritus, rash, nausea, vomitingHypersensitivity (e.g., anaphylaxis).If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occurs, immediately discontinue administration and initiate appropriate medications and/or supportive care. Infusion-related reactions may include: fever, difficulty breathing, reduced oxygen saturation, chills, fatigue, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), chest pain or discomfort, weakness, altered mental status, nausea, headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, vaso-vagal reactions (e.g., pre-syncope, syncope), dizziness, and diaphoresis. If an infusion-related reaction occurs, administer appropriate medications and/or supportive care. Patients should be observed for at least 1 hour after injection is complete.Prescribing health care provider and/or provider’s designee are/is responsible for mandatory reporting of all medication errors and serious adverse events potentially related to bebtelovimab within 7 calendar days from the onset of the event. Please review the fact sheet for healthcare providers: EUA of bebtelovimab for instructions on how to submit adverse event reports to FDA MedWatch. | Dysgeusia, diarrhea, hypertension, myalgia. Hepatic transaminase elevations, clinical hepatitis, and jaundice have occurred among patients receiving ritonavir. Thus, caution should be exercised when administering nirmatrelvir-ritonavir to patients with pre-existing liver diseases, liver enzyme abnormalities, or hepatitis. There may be a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection due to the co-administration of nirmatrelvir and ritonavir. Prescribing healthcare provider and/or provider’s designee are/is responsible for mandatory reporting of all serious adverse events\* and medication errors potentially related to nirmatrelvir-ritonavir within 7 calendar days from the onset of the event, using FDA form 3500. Please review the fact sheet for healthcare providers: EUA of nirmatrelvir/ritonavir for instructions on how to submit adverse event reports to FDA MedWatch. | Diarrhea, nausea, dizziness  Prescribing healthcare provider and/or provider’s designee are/is responsible for mandatory reporting of all serious adverse events\* and medication errors potentially related to molnupiravir within 7 calendar days from the onset of the event, using FDA form 3500. Please review the fact sheet for healthcare providers: EUA of molnupiravirfor instructions on how to submit adverse event reports to FDA MedWatch. |

\*Serious adverse events are defined as: death or a life-threatening adverse event; a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or a congenital anomaly/birth defect

1. Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of remdesivir. Updated October 2021.

2. Gottlieb RL, Vaca CE, Paredes R et al. Early remdesivir to prevent progression to severe COVID-19 in outpatients. *New England Journal of Medicine* 2021.

3. Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of sotrovimab. Updated November 2021.

4. Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of bebtelovimab. Updated February 2022.

5. Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of nirmatrelvir-ritonavir. Updated December 2021.

6. Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of molnupiravir. Updated December 2021.