Management Guideline for Non-Hospitalized High-Risk Patients with COVID 19 – RCHSD August 2022

Current options for treatment (and for some drugs, prophylaxis) of non-hospitalized high-risk patients with COVID 19 include antiviral therapy (nirmatrelvir-ritonavir (Paxlovid) oral, remdesivir IV, molnupiravir oral) as well as monoclonal antibody (bebtelovimab, tixagevimab-cilgavimab) therapy. All antiviral agents retain activity against the current B2, B4, B5 omicron variants however of monoclonal antibody products available for treatment of COVID 19, only bebtelovimab and tixagevimab-cilgavimab appear to maintain reasonable activity against this variant. Currently only remdesivir is FDA approved. Other treatments are only authorized under Emergency Use Authorization and are not FDA approved. The authorizations include non-hospitalized patients with laboratory confirmed SARS CoV2 infection, with mild to moderate disease, early in the disease course (5-10 days), and with high risk for progression to severe disease or hospitalization (See EUA fact sheet for healthcare providers for specific drug). High risk patients hospitalized for non-COVID related indications but are actively infected, may also be candidates.

For pediatric patients, limited data on efficacy and safety of treatments are available. Remdesivir treatment for children under 12 years (but at least 3.5 kg) is approved, however treatments are only authorized for patients 12 years and older (18 years for molnupiravir) and $\geq$40 kg.

Considerations for treatment include the following:

1. Patient age, weight and clinical risk factors with highest priority given to patients at highest risk.
2. Availability of treatment.
3. Feasibility of treatment as remdesivir and monoclonal antibody therapy require intravenous infusion.
4. Activity against circulating COVID 19 variants. In terms of efficacy against the current omicron variants, NIH guidelines rank therapy in the following order: nirmatrelvir-ritonavir (Paxlovid), remdesivir, bebtelovimab, and molnupiravir (over age 18 years).

For those products that have FDA EUA and not full approval, – Please review the EUA Fact Sheet for Healthcare Providers, and review the EUA Fact Sheet for Patients with the family. No signed consent is required.

Patient risk group prioritization:

Tier 1 – Immunocompromised* individuals not expected to mount an adequate immune response to COVID 19 vaccination or SARS CoV2 infection due to their underlying conditions, regardless of vaccine status

Tier 2 – Unvaccinated individuals with clinical risk factors** for severe disease not in Tier 1

Tier 3 - Vaccinated individuals with clinical risk factors** for severe disease. Priority for unboosted patients.

***Immunocompromising Conditions**

(unlikely to mount an adequate response to COVID 19 vaccination or SARS CoV2 infection and at risk for severe outcomes)

1. Patients within 1 year of receiving B cell depleting therapies (eg. Rituximab, ocrelizumab, ofatumumab, alemtuzumab)
2. Patients receiving Bruton tyrosine kinase inhibitors
3. Chimeric antigen receptor t cell recipients
4. Post HSCT with chronic GVHD or are taking immunosuppressive medications for another indication
5. Patients with hematologic malignancies on active therapy
6. Lung and cardiac transplant recipients
7. Patients within 1 year of receiving other solid organ transplant (SOT) (eg. kidney, liver)
8. SOT recipients with recent treatment for acute rejection with T or B cell depleting agents
9. Patients with SCID
10. Patients with untreated HIV with CD4 T lymphocyte cell count <200 cells/mm3

****Clinical risk factors (See AAP statement referenced below):**

1. Immunocompromising conditions or receipt of immunosuppressive medications
2. Obesity (BMI>85th percentile)
3. Age < 1 year, particularly with prematurity and/or other comorbid conditions such as lung disease. (most patients under 1 year of age with COVID 19 do not require treatment).
4. Cardiovascular disease/congenital heart disease
5. Chronic kidney disease
6. Chronic lung disease/Asthma
7. Chronic liver disease
8. Medical related technological dependence not related to COVID 19 (eg. Tracheostomy, PPV, gastrostomy)
9. Diabetes mellitus
10. Pregnancy
11. Sickle Cell disease
12. Genetic/Neurodevelopmental disorders with medical complexity (eg. trisomy 21, cerebral palsy, neuromuscular disease)

The likelihood of severe disease increases with multiple comorbidities.

Treatment options:

	Class	Dose	Route	Age	Weight	Other
Nirmatrelvir-ritonavir (Paxlovid)	Antiviral	300 mg nirmatrelvir 100 mg ritonavir BID x 5 days	Oral	≥12 year	≥40 kg	Drug interactions associated with CYP3A metabolism *Renal Paxlovid available for patients with GFR >30 to <60 mL/min
Bebtelovimab	Monoclonal Ab	175 mg	IV	≥12 year	≥40 kg	1 minute infusion, 1-hour post-infusion observation required
Remdesivir	Antiviral	200 mg x 1 day, then 100 mg daily x 2days	IV	≥12 year	≥40 kg	Currently for RCHSD patients, remdesivir is being given in SIDU or PICU.
		5 mg/kx 1 day, then2.5 mg/kg once daily x 2 days	IV	< 12 year	≥3.5 kg	
Molnupiravir	Antiviral	800 mg BID x 5 days	Oral	≥18 year		Not available at RCHSD pharmacy

Pre-exposure Prophylaxis:

	Class	Dose	Route	Age	Weight	Other
Tixagevimab-cilgavimab (Evusheld)	Monoclonal Ab	300 mg every 6 months	IM	≥12 year	≥40 kg	

How to order treatment:

1. Determine which treatment, if any, is appropriate for the patient. Infectious Diseases is available to discuss which treatment options might be best for the patient.
2. Bebtelovimab requires ID approval and one hour observation following administration.
3. Nirmatrelvir/ritonavir (Paxolovid) and molunupiravir are available through CVS and other outpatient pharmacies. RCHSD outpatient pharmacy has nirmatrelvir/ritonavir (Paxlovid). We recommend calling to confirm availability. COVID Therapeutics Locator
4. Check for drug interactions. COVID Therapeutics Drug Interaction Checker
5. Medications on Emergency Use Authorization (EUA) require distribution of Fact Sheet for Patients and Caregivers.

References:

1. AAP COVID 19 Interim Guidance. Management Strategies in Children and Adolescents with Mild to Moderate COVID 19. 12/27/2021 (https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/outpatient-covid-19-management-strategies-in-children-and-adolescents/)
2. NIH COVID 19 Treatment Guidelines, https://www.covid19treatmentguidelines.nih.gov/.
3. The COVID-19 Treatment Guidelines Panel's Statement on Therapies for High-Risk, Nonhospitalized Patients With Mild to Moderate COVID-19, Dec 30, 2021
4. The COVID-19 Treatment Guidelines Panel's Statement on Potential Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications, Dec 30,2021
5. The 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, Dec 23, 2021
6. Fact Sheet for Healthcare providers: Emergency Use Authorization for Paxlovid™
7. Fact Sheet for Healthcare providers: Emergency Use Authorization for Molnupiravir
8. Kompaniyets L, et al. Underlying Medical Conditions Associated with Severe COVID 19 Illness Among Children JAMA Network Open June 2021.
9. Gottlieb RL, et al. Early remdesivir to prevent progression to severe Covid 19 in outpatients, NEJM 2021.