Management Guideline for Non Hospitalized High Risk Patients with COVID 19 – RCHSD January 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 (bamlanivimab-etesevimab, casirivimab-imdevimab, sotrovimab, tixagevimab-cilgavimab) therapy. All antiviral agents retain activity against the omicron variant however of monoclonal antibody products available for treatment of COVID 19, only sotrovimab appears to maintain reasonable activity against this variant. These 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).

For pediatric patients, little data on efficacy and safety of treatments are available. Options are further limited because most of the treatments are authorized for patients 12 years and older(18 years for molnupiravir) and ≥40 kg. Bamlanivimab/etesevimab is the only monoclonal antibody product authorized for children <12 years of age. It is an option for therapy with the understanding that activity against the omicron variant is likely poor but activity remains against other variants. Remdesivir treatment for children under 12 years (but at least 3.5 kg) has been given FDA authorization (EUA) for hospitalized children.

Not all patients with a clinical risk factor is necessarily a candidate for treatment. Both antiviral therapy and monoclonal antibody therapy are in limited supply and treatment considerations are based on 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 sotrovimab require intravenous infusion.
4. Activity against circulating COVID 19 variants. In terms of efficacy against the omicron variant, NIH guidelines rank therapy in the following order: nirmatrelvir-ritonavir (Paxlovid), sotrovimab, remdesivir and molnupiravir.

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.

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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
Sotrovimab	Monoclonal Ab	500 mg	IV	≥12 year	≥40 kg	
Remdesivir	Antiviral	200 mg x 1 day, then 100 mg daily x 2 days	IV	≥12 year	≥40 kg	
		5 mg/kg on Day 1 followed by 2.5 mg/kg once daily x 4	IV	< 12 year	≥3.5 kg	
Molnupiravir	Antiviral	800 mg BID x 5 days	Oral	≥18 year		

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. Both sotrovimab and remdesivir options may require ID approval and admission to the SIDU (inpatient COVID unit) to be given.
3. Nirmatrelvir with ritonavir (Paxolovid) and molunupiravir are available through CVS and other outpatient pharmacies, but initial distribution did not include hospitals. We recommend calling to confirm availability. RCHSD currently does not have either drug in stock, but we have ordered for both inpatient and outpatient pharmacies.

References:

4. 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/)
5. NIH COVID 19 Treatment Guidelines, https://www.covid19treatmentguidelines.nih.gov/.
6. The COVID-19 Treatment Guidelines Panel's Statement on Therapies for High-Risk, Nonhospitalized Patients With Mild to Moderate COVID-19, Dec 30, 2021

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7. The COVID-19 Treatment Guidelines Panel's Statement on Potential Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications, Dec 30,2021
8. 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
9. Fact Sheet for Healthcare providers: Emergency Use Authorization for Paxlovid™
10. Fact Sheet for Healthcare providers: Emergency Use Authorization for Molnupiravir
11. Kompaniyets L, et al. Underlying Medical Conditions Associated with Severe COVID 19 Illness Among Children JAMA Network Open June 2021.
12. Gottlieb RL, et al. Early remdesivir to prevent progression to severe Covid 19 in outpatients, NEJM 2021.